Article

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L-Selectin and Adiponectin as Novel Biochemical-Immune Markers for the Response of Infertile Polycystic Ovary Syndrome Patients to Metformin Treatment

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women throughout their lifespan. The prevalence of PCOS varies depending on the population studied, but it is estimated to affect between 10% and 13% or ~140 million women globally. PCOS in adults is diagnosed according to the International Evidence-based Guideline Criteria based on two of either ovulatory dysfunction, clinical or biochemical hyperandrogenism, and/or polycystic ovary morphology (PCOM) on ultrasound or elevated anti-Müllerian hormone levels. Infertility is a serious global health problem affecting an estimated 50 to 70 million couples worldwide. Infertility is a condition in which pregnancy does not occur even after regular unprotected sex for more than one year و for women under 35 years of age, a couple's failure to conceive after 12 months of regular sexual activity without using contraception, and after 6 months for women 35 years of age or older. Infertility results in disability expressed through impaired function, social exclusion, and psychological trauma; thus, it is ranked by the World Health Organization as the fifth highest serious disability worldwide. **Population of the study:** This study included samples of 90 women of reproductive age (20-40 years). They were distributed into three groups. The first: included 30 patients undergoing treatment for infertility due to PCOS, the second group included 30 patients who were diagnosed with PCOS through the simultaneous appearance of 3-4 symptoms that are essential for diagnosis. The third group (the control group) included 30 women who were completely free of symptoms of PCOS and all of whom had children without any medical intervention and did not suffer from any disease, based on clinical examinations and ultrasound examinations. **Kits and technique:** Sandwich-ELISA technique was applied to determine the level ofL-Selectin and Adiponectin in the serum samples of the study individuals. **Results:** Respectable statistical differences in L-Selectin levels were observed when comparing the group of PCOS patients treated with infertility drugs (p=0.000) and those with Untreated PCOS

patients group as well as the members of the control group (p=0.000).The results showed a significant increase in adiponectin levels when comparing the three study groups together (p=0.000).The present data indicate a moderately positive correlation between L Selectin and adiponectin in PCOS patients treated with infertility drugs (r=0.408 at p=0.048), and healthy women (r=0.641 at p=0.046)the indicate a very weak and practically insignificant negative correlation between L-Selectin and adiponectin in the untreated PCOS group (r=0.168 at p=0.228). The study showed the highest sensitivity (97%) and specificity (97%) for adiponectin were recorded in the Metformin-treated group. The study revealed that adiponectin exhibited the highest individual sensitivity (93%) and specificity (97%) in the group of untreated PCOS patients. **Conclusions:** L-Selectin and adiponectin are promising tools for differentiating PCOS patients treated with Metformin and untreated PCOS patients.

Key Words PCOS, Infertility, Metformin, L-Selectin and Adiponectin

Introduction

Polycystic ovary syndrome (PCOS) is a complex common endocrine disorder affecting around 5–20% of reproductive aged women, depending on the diagnostic criteria used and population studied [1]. PCOS is characterized by hyperandrogenism, oligoovulation and/or polycystic ovaries, is a very common endocrine and metabolic disorder with an increased risk of reproductive abnormalities, often accompanied by insulin resistance (IR) [2]. PCOS is a heterogeneous condition that can cause a variety of reproductive, metabolic, and psychological effects, and its severity may vary between individuals depending on factors such as age, diet, race, genetics, medications, contraceptive use, obesity, body mass index, and geographic region [3]. PCOS is recognized as the leading cause of anovulatory infertility, accounting for approximately 70% of infertility cases related to ovulation disorders [3]. Hyperandrogenism in women with PCOS can be detected clinically by evaluation of hirsutism, acne, or androgenic alopecia, or by biochemical testing of circulating androgen concentrations [4].Worldwide, the prevalence of PCOS ranges from 4% to 21% [5]. The prevalence of PCOS varies widely worldwide. A recent meta-analysis examining the prevalence of PCOS in women of reproductive age across different ethnic groups worldwide indicated that women in the Middle East had one of the highest prevalence rates, at 16.0% [6]. A comprehensive analysis of the Middle East and North Africa (MENA) region revealed an overall prevalence of clinical infertility of 7.2% [6]. Considering all studies, the prevalence of PCOS was 4.98% according to the NIH 1990, 8.80% according to the Rotterdam 2003, 4.74% according to the AE-PCOS 2006, and 1.69% according to other criteria/self-report, with an overall PCOS prevalence of 4.57%. All studies using the NIH 1990, Rotterdam 2003, and AE-PCOS 2006 were of high quality, and those using other criteria/self-report were of low quality, so subgroup analysis based on quality resulted in the same prevalence rates as above [7]. The main cause of infertility in Iraqi Arab women is PCOS, which accounts for about 46% of all infertility cases. The prevalence of PCOS appears to be increasing due to changes in lifestyle, nutrition, and obesity. This confirms the findings in other studies where prevalence studies were classified by geographic location. It should also be noted that even within the same ethnic group, *i.e.* Middle

Eastern women [8].There is a lack of comprehensive research on the prevalence of PCOS in Iraq. The recent study conducted in Erbil, the only local investigation available, focused on infertile women seeking assistance at an *in vitro* fertilization (IVF) center, using the Rotterdam 2003 criteria for diagnosis, and the results revealed a prevalence of PCOS of 33% among the participants [9].L-Selectin is a type I transmembrane glycoprotein expressed on leukocytes[10] also known as CD62L, is an important cell adhesion molecule and is pivotal to immune function and leukocyte movement within the human body [11]. L-Selectin is a member of the family of adhesion molecules expressed on leukocytes, plays a key role in lymphocyte homing and migration and neutrophil recruitment to sites of inflammation [12,13]. It is an adhesion molecule on the surface of granulocytes, monocytes, and naive T cells, which is enzymatically cleaved (shed) upon cell activation and plays a role in lymphocyte-endothelial cell interaction. The expression of this molecule on the cell surface can be measured by fluorescently labeled anti-CD62L antibodies using flow cytometry [12]. By interacting with endothelial cell ligands, L-Selectin facilitates the initial binding and circulating of leukocytes along the vascular wall, promoting their extravasation into lymphoid tissue and sites of inflammation[11]. The new evidence suggests that L-Selectin is a key player in regulating monocyte protrusion during migration across endothelial cells [13]. It is also known for its role in white blood cells in mediating binding and rolling [14].

Adiponectin is a hormone secreted by adipose tissue (white adipocytes, WAT), it positively modulates the endocrine system and increases insulin sensitivity both in healthy individuals and in disorders of glucose and lipid metabolism. WAT not only serves as an energy store, but also as a glandular organ, secreting adiponectin, which enhances insulin sensitivity and exerts anti-inflammatory effects. Furthermore, adiponectin promotes the conversion of white adipocytes into metabolically active beige adipocytes, enhancing overall energy expenditure and providing protective effects against obesity and metabolic disorders [15]. Blood adiponectin concentrations are influenced by many factors such as age, body weight, percentage of adipose tissue, and in particular diet [16]. Interestingly, gender appears to influence adiponectin levels: several studies have shown higher levels of adiponectin in women than in men, possibly due to higher levels of estrogen, which is known to affect adipose tissue [17].

Adiponectin is a protein that regulates a number of metabolic diseases, including diabetes, dyslipidemia, atherosclerosis, and the metabolic dysfunction that occurs in cardiovascular diseases such as hypertension. Several studies have suggested that altered levels of adiponectin in plasma and cerebrospinal fluid are consistent with a distinct state of mild cognitive impairment (MCI) and Alzheimer's disease [18].

Materials and Methods

The Population: Over a period of five months, from October 2024 to March 2025, 90 women participated in the current study. These participants were divided into three groups.

The first group included 30 samples from patients undergoing infertility treatment with metformin, collected from the Fertility Center - Al-Sadr Medical City in Najaf Governorate.

The second group included 30 samples from patients with PCOS who had been diagnosed with infertility and had not received any treatment at all. These samples were collected from Al-Zahraa Teaching Hospital and Al-Furat Al-Awsat Hospital. The study included patients with primary or secondary infertility due to PCOS, aged 20–40 years.

The third group included 30 healthy women with normal testosterone levels, regular menstrual cycles, normal ovulation, healthy ovaries, natural childbearing without surgical intervention, no use of contraception, no history of PCOS, and within the study age group (20-40 years). Samples of Control group were collected from a hospital work environment, in addition to graduate students at the College of Education for Girls and their relatives.

Inclusion Criteria:.The current study included the participation of patients characterized by the following:

- **Symptoms of the Syndrome:** the patients must exhibit at least 3-4 symptoms of PCOS.
- **Physiological Puberty:** the participating patients must have normal puberty and not suffer from primary amenorrhea, before symptoms of the PCOS appear.
- **Marital Status:** all patients must be married for at least one year and suffer from primary or secondary infertility due to PCOS.
- **Age:** the age of participants (patients and controls) must be at least 20 years old, and no more than 4o years old.

Exclusion Criteria: a number of females were excluded, which included: Unmarried, pregnant women, females (patients or controls) who use contraceptives, menopause females, female patients who suffered from cancerous or chronic disease (diabetes, cardiovascular diseases and hypothyroidism), females with autoimmune diseases, smokers.

Assessment of Lectins Concentration: Sandwich enzyme linked immune sorbent assay (Sandwich-ELISA) method was applied to determine the level of L-Selectin and Adiponectin in the serum samples of the study individuals.

The Statistical Analysis of the Data: The outcomes of the present study were analyzed through the statistical package for the social sciences (SPSS) version 26 software application statistical analysis system and excel (statistical package). The variables were illustrated by mean ± S.D, minimum, maximum, frequencies, and percentages. Graphics are presented using pie and bar charts. Inferential data analysis includes analysis of variance (ANOVA) test was applied to assess differences between the levels of the studied parameters. Pearson's correlation was applied to determine the relation among the parameters of the present study.The probability of deflection than controls are considered statistically significant if *p*-value is below 0.05. Receiver operating characteristic (ROC) curve was applied to present the sensitivity of the evaluated parameters. Combined sensitivity and specificity percentages were calculated according to biomedical statistical.

Results and Discussion

- **Assessment of L-Selectin in the Sera Samples of the Study Groups** The levels of L-Selectin were evaluated in the study samples, it was found that the highest mean of L-Selectin (4.279 ng/mL) which was recorded in G1, while its lowest levels (3.144 ng/mL) was noted in G2. The statistical analysis by means of the ANOVA test has showed that there are significant statistical differences (p=0.000) when comparing the group of PCOS patients treated with infertility drugs and those with Untreated PCOS patients group as well as the members of the control group (p=0.000), while the statistical significance is absent in the comparison between the levels of L-Selectin in the Untreated PCOS patients group and those in the control group (p=0.063), as shown in **Table 1**.

Table 1: L-Selectin Levels in the Serum Samples of the Studied Groups

Subjects (n)	L-Selectin *(µg/mL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 PCOS Patients (30)	**4.279±0.651**	**2.50-5.55**	**0.000 For G1 *vs* G2 0.000 For G1 *vs* C 0.063 For G2 *vs* C**
G2 PCOS Patients (30)	**3.144±0.613**	**1.97-4.09**	
Controls (30)	**3.520±0.988**	**2.09-5.67**	

G1: Group of PCOS patients treated with infertility drugs, G2: Untreated PCOS patients group and Controls: A group of healthy individuals. The mean difference is significant at the 0.05 level.

Selectins are adhesion molecules represented by three types of selectins: L-Selectins, P-Selectins, and E-Selectins. Type I transmembrane glycoproteins mediate the interaction between hematopoietic cells and the endothelial surface [19].The carbohydrate-binding L-Selectins are localized in the endometrial epithelium at the time of implantation [20]. L-Selectin is strongly expressed in the trophectoderm of hatched blastocysts to facilitate their binding to the uterine epithelium. Conversely, blocking L-Selectin with antibodies suppresses embryo implantation. Furthermore, L-Selectin is expressed in the human endometrium during both the natural and stimulated cycle. A cyclic expression pattern of L-Selectin was observed during the human menstrual cycle, in which glandular epithelial expression was higher in the mid-secretory phase of the cycle [20]Previous studies have shown that L-Selectin expression on the blastocyst and its interaction with oligosaccharide ligands on the surface of the maternal uterine cavity are key factors in embryo attachment to the uterus. L-Selectin ligands are located in the lumenal and glandular epithelium of the uterus, and their expression increases during the period of uterine receptivity [21].L-Selectin acts on rolling leukocytes to amplify inflammatory responses by binding to ligands, particularly PSGL-1, on circulating neutrophils, leading to leukocyte aggregation and secondary capture. In addition to its role in innate immune responses, L-Selectin functions as a mediator of leukocyte transport between the blood and lymph. High endothelial venule cells in lymph nodes express sulfated glycoproteins that bind to L-Selectin on circulating leukocytes, enabling the transport of lymphocytes from the blood to the lymph nodes. This transport is vital for immune surveillance, as it enables circulating

lymphocytes to reach antigen-presenting cells in lymphoid tissue [22]. L-Selectin plays a key role in early embryo attachment and adhesion [23]. Decreased epithelial expression of the ligand has been associated with infertility, while increased L-Selectin expression has been implicated in ectopic pregnancies [9].The fallopian tube competes with the uterus to transmit signals consisting of L-Selectin, muscle proteins, cytokines, chemokines, and adhesion molecules. The embryo's inability to properly locate, attach, and invade the endometrium results in its migration and implantation in the fallopian tube [24]. A preliminary study showed that ovarian stimulation with letrozole resulted in a sevenfold increase in the expression of uterine receptive markers, including integrins, leukemia inhibitory factor, and L-Selectin, in women with unexplained infertility compared to those with normal cycles [12,25].A previous study of 90 individuals, 45 with PCOS and 45 healthy controls, showed significantly lower L-Selectin levels in the PCOS group. This finding may be related to significant hormonal imbalances, particularly elevated androgen levels. These hormonal changes can affect the immune system and the expression of various cell surface molecules [9].The current study demonstrated a significant increase in L-Selectin levels in the PCOS group during infertility treatment. This suggests that metformin or letrozole and a low-carbohydrate diet improve endometrial function in PCOS patients. Metformin also stimulates ovulation and improves ovarian response. A decrease in L-Selectin levels was observed in the untreated PCOS group. This was due to increased LH and decreased FSH levels, as well as increased androgen levels. These hormonal changes can affect the immune system.

- **Assessment of Adiponectin in the Sera Samples of the Study Groups:**Adiponectin levels were appraised in samples of participants in the current study. It was noted that adiponectin concentration increases in the patient groups compared to healthy individuals, moreover; the highly elevations of this parameter was shown in the PCOS patients treated with infertility drugs, Statistically, highly significant differences were illustrated when the three study groups compared together **(p=0.000)**, as shown in **Table 2**.

Table 2: Levels Adiponectin in the Serum Samples of the Studied Groups

Subjects (n)	**Adiponectin*(ng/mL)* *Mean ± SD***	***Minimum-Maximum***	***p-value***
G1 PCOS Patients (30)	**109.572±13.885**	**87.88-134.57**	**0.000 For G1 *vs* G2** **0.000 For G1 *vs* C** **0.000 For G2 *vs* C**
G2 PCOS Patients (30)	**94.363±8.759**	**75.64-110.55**	
Controls (30)	**78.461±11.238**	**43.25-95.19**	

G1: Group of PCOS patients treated with infertility drugs, G2: Untreated PCOS patients group and Controls: A group of healthy individuals. The mean difference is significant at the 0.05 level.

Adiponectin (ADPN) is a monomeric protein, synthesized and secreted in white adipose tissue [26]. Adiponectin consists of 244 amino acids and has a molecular weight of 28 kDa in humans [27]. Adiponectin and its receptors (AdipoR1 and AdipoR2) are found in human ovarian cells (oocytes, granulosa cells, follicular membrane cells, and accumulation cells) and

human follicular fluid at different stages of follicular development. Adiponectin receptors were also found in placental and endometrial cells, suggesting that this adipokine might play a crucial role in embryo implantation, trophoblast invasion and fetal growth. Adiponectin controls the steroidogenesis of ovarian granulosa cells and has also been shown to decrease the production of progesterone and androstenedione in insulin-induced follicular theca cells [28].

Adipo-R1 mRNA expression is positively correlated with insulin, triglyceride, cholesterol, and testosterone levels. Tissues treated with testosterone and estradiol have been found to increase the expression of these receptors. Increased adiponectin receptors have also been reported in patients with polycystic ovary syndrome [29].

In addition to being expressed in the ovaries, adiponectin has also been found to be expressed in the hypothalamus and pituitary gland. Short-term treatment with recombinant adiponectin can inhibit gonadotropin-releasing hormone (GnRH) secretion by activating AMP-activated protein kinase (AMPK), thereby reducing luteinizing hormone secretion [28].

The primary function of adiponectin is to increase tissue sensitivity to insulin and reduce hepatic glucose production. Obesity, in which adiponectin levels are low, leads to increased insulin resistance and hyperinsulinemia, which stimulates the production of androgens in the ovaries, disrupting hormonal balance. Insulin resistance is one of the mechanisms underlying the development of PCOS, which is often associated with excess body weight. Furthermore, insulin resistance can directly affect the HPG axis. By altering GnRH, FSH, and LH pulsations, it leads to menstrual irregularities and may even cause anovulation [30, 31]. Alpha adiponectin regulates reproductive function by influencing ovarian steroidogenesis and folliculogenesis, contributing to the regulation of ovulation and fertility[30].

Adiponectin serves as a key link between energy metabolism and reproductive processes, highlighting the complex interplay between adipose tissue and reproductive physiology. Suboptimal reproductive health, such as irregular menstrual cycles or PCOS, can lead to an imbalance of hormones involved in metabolism. In conditions such as PCOS, alterations in insulin sensitivity and ovarian function can lead to decreased adiponectin levels, contributing to metabolic disturbances and exacerbating reproductive dysfunction [32, 33]. Sibilian, Yildiz, and colleagues also found a significant negative association between serum adiponectin levels and IR in women with PCOS, but they used a small sample size and performed only a simple correlation analysis of serum adiponectin levels and IR in their studies [32].

Others have reported similar adiponectin levels in BMI-matched PCOS patients and their controls. They attributed this changes to fat distribution and variable amount of sub-cutaneous and high visceral fat [33]. Recently, there has been growing interest in identifying changes in circulating adipokine levels in women with polycystic ovary syndrome. Elevated serum adiponectin levels have been observed [34]. Moreover, it was observed that key downstream regulatory molecules associated with adiponectin signalling, such as APPL1 and APPL2, are altered in endometria from women with obesity and IR, with or without PCOS. Importantly, MTF oral treatment was capable of restoring the levels of these molecules to basal conditions, suggesting a positive effect of MTF in insulin and adiponectin signalling pathways in human endometrial cells. Probably, the effect of MTF in women with PCOS is mainly related to the

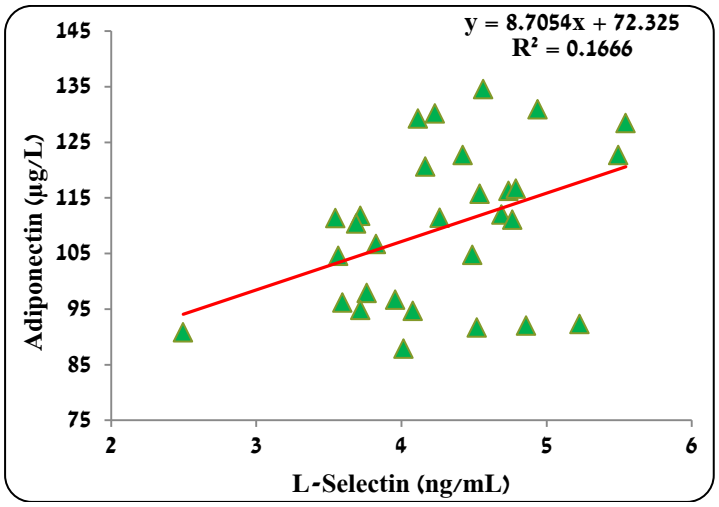
improvement of inflammatory parameters associated with obesity. In this regard, one study showed that MTF increases circulating adiponectin [35].

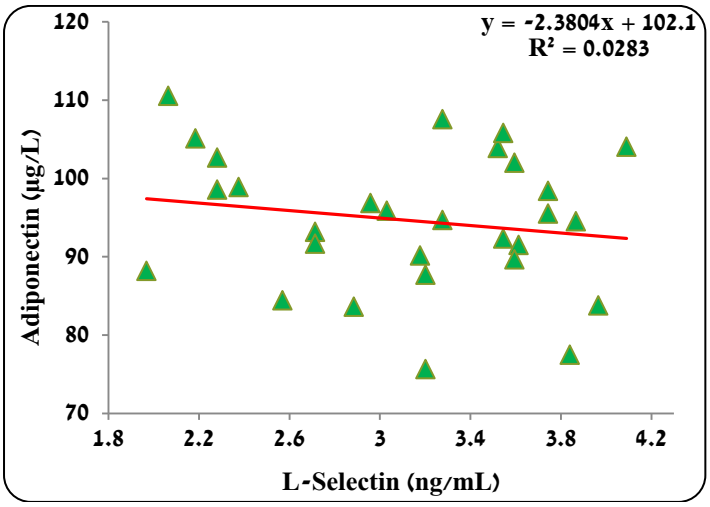
In the current study, an increase in the adiponectin levels was observed, which is considered a biomarker of metformin's effectiveness in PCOS patients. Increased adiponectin levels with treatment are associated with improved metabolic and reproductive symptoms.

- **The Relationship among the New Evaluated Parameters in the Study Individuals:** The relationships among the new evaluated criteria (L-Selectin and adiponectin) were tested for the members in the study groups**.**

- **The Correlation between L-Selectin and Adiponectin in PCOS patients treated with infertility drugs and Untreated PCOS patients in addition to Healthy Control Group**

The present data indicate a moderately positive correlation between L-Selectin and adiponectin in PCOS patients treated with infertility drugs (r=0.408 at p=0.048), and healthy women (r=0.641 at p=0.046). as shown in **Figures 1 A** and **3 C** respectively. According to the data in **Figure 1 B**, the indicate a very weak and practically insignificant negative correlation between L-Selectin and adiponectin in the untreated PCOS group (r=0.168 at p=0.228). L-Selectin can explain only a very small proportion of the variance in adiponectin levels.





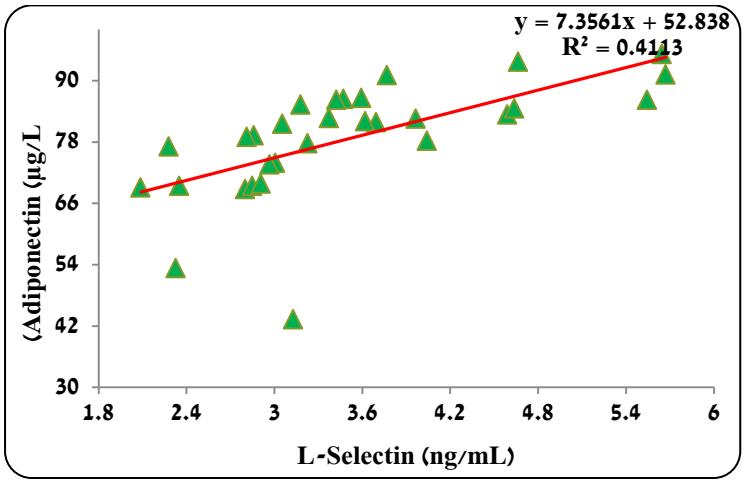


Figure 1: Relationship of L-Selectin and Adiponectin in: (A) G1 Patients Group (B) G2 Patients Group and (C) Healthy Individuals Group

- **Sensitivity and Specificity of the Evaluated Parameters**

Sensitivity is known as the true positive rate or the probability of detection, it measures the proportion of positives that are correctly identified. Specificity is known as the true negative rate; it measures the proportion of negatives that are correctly identified. The calculation of sensitivity and specificity is used for assessing the efficiency of the tested parameters to suggest them as diagnostic markers. The diagnostic efficiency of the included criteria in this work were evaluated by applying the receiver operating characteristic (ROC) as demonstrated **in Figurers 3, 4**and**5**L-Selectin and Adiponectin; respectively.

Table 3 shows the area under the curve and cut-off values for the criteria evaluated in the current study. The study demonstrates the efficacy (sensitivity) of the criteria evaluated in the current study in distinguishing between PCOS patients treated with Metformin and those not treated. The study showed the highest sensitivity (97%) and specificity (97%)for Adiponectin were recorded in the Metformin-treated group.

Table 3: Receiver Operating Characteristic Analysis of L-Selectin and Adiponectinas Prognostic Markers for Polycystic Ovary Syndrome Patients Treated with Infertility Drugs

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
L-Selectin	0.837	0.044	0.000	3.713	93	90	0.750-0.924
Adiponectin	0.982	0.013	0.000	90.266	97	97	0.957-1.000

AUC: Area Under Curve, SE: Standard Error

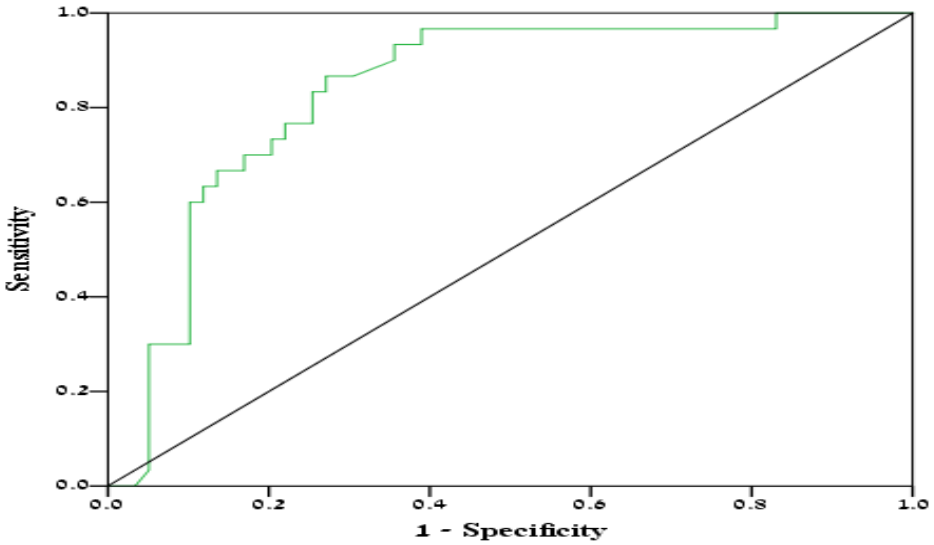


Figure 2: Receiver Operating Characteristic Curve of L-Selectin in G1 Polycystic Ovary Syndrome Patients

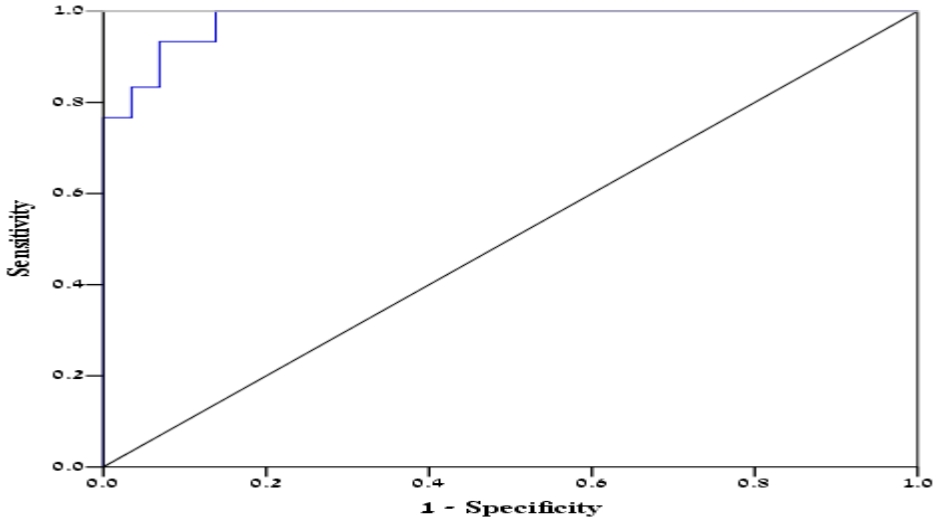


Figure 3: Receiver Operating Characteristic Curve of Adiponectin in G1 Polycystic Ovary Syndrome Patients

The combined sensitivity of L-Selectin and Adiponectin parameters was examined in the current study, as summarized in Table 4. The results of the study demonstrate the highest sensitivity (100%) when combining two parameters evaluated together.

Table 4: The Combined Sensitivity of the Evaluated Parameters

Parameters	Adiponectin
L-Selectin	100

Table 5 presents the area under the curve and cut-off values for the criteria assessed in this study. This research demonstrates the effectiveness (sensitivity) of these criteria in differentiating between untreated and treated PCOS patients. The study revealed that adiponectin exhibited the highest individual sensitivity (93%) and specificity (97%) in the group of untreated PCOS patients.

Table 5: Receiver Operating Characteristic Analysis of L-Selectin and Adiponectin as Diagnostic Markers for Polycystic Ovary Syndrome Patients

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
L-Selectin	0.422	0.076	0.303	3.049	47	47	0.274-0.570
Adiponectin	0.889	0.042	0.000	89.056	93	97	0.806-0.971

AUC: Area Under Curve, SE: Standard Error

When the combined sensitivity was calculated, the combination of L-Selectin and adiponectin yielded a value of 97, as seen at their intersection, as shown in **Table 6.**

Table 6: The Combined Sensitivity of the Evaluated Parameters

Parameters	Adiponectin
L-Selectin	97

Conclusions

L-Selectin and adiponectin are promising tools for differentiating PCOS patients treated with infertility drugs and Untreated PCOS patients.

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