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ASSESSMENT OF SERUM SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (SUPAR) AS A POTENTIAL RISK MARKER IN OBESE WOMEN WITH PREDICTIVE MARKER FOR POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Background: Polycystic ovarian syndrome, or PCOS, is a common metabolic and endocrine disorder. It affects 5–15% of reproductive-age females. Genetic, environmental, and behavioural variables combine in the complex etiopathogenesis of PCOS.

SuPAR, also called circulating uPAR, is a glycosyl-phosphatidylinositol-anchored (GPI) receptor protein with three domains (DI, DII, and DIII) that is encoded by the Plaur gene and expressed on a variety of immune cells. SuPAR has been identified as a possible predictive biomarker for a number of inflammatory illnesses due to its ability to imitate local inflammation and immune response.

Objective : Assessment serum of soluble urokinase plasminogen activator receptor (suPAR) level in Iraqi PCOS patients as a potential of risk marker.

Patients and Methods: One hundred eighty Iraqi women for progressing of PCOS with aged range between 20–40 years. Ninety well-diagnosed PCOS patients and ninety healthy fertile women served as the control group in an age-matched case-control study design. The groups were gathered between December 2023 and March 2024 from private laboratories and the Al-Sadr Teaching Hospital, Al-Hakeem Hospital, and Al-Zahraa Hospital in the Najaf Governorate. An enzyme-linked immunosorbant assay (ELISA) was used to test each subject's reproductive hormones (LH, FSH, TT, and TF) and suPAR level. The results were analysed with appropriate statistical methods.

Results: The patient women with PCOS had significantly higher of BMI ,LH, LH/FSH ratio, TT,FAI, FIN, FSG,and, HOMA-I R women than the healthy women group. the result demonstrates that suPAR level significantly higher in PCOS patients group ($P < 0.0001$) when compared with healthy control group. ((**2.0745±0.4102)) vs(1.0442±0.3894, p<0.0001)** respectively. Furthermore, PCOS patients in this study had significantly higher serum suPAR levels ($P = 0.0001$). examine the influence of serum suPAR levels on the biochemical parameters in patients women with the PCOS is evaluated by the

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correlation coefficient However, Significant negative correlation were obtained between suPAR levels and IL-39 , SHBG ,FSH.While, significant positive correlation are illustrated between levels BMI,WHRM, LH, LH/FSH, TT, FIA, FSG, FIN, HOMA-IR, HOMA-%β, TG, and age with serum levels of suPAR in the patient group..suPAR had an AUC of 97.1 [95%CI (confidence interval) = 0.94-1.000, Sensitivity = %91.3, Specificity = %91.1, Cut-off point = 1.775 ng/ml].

Conclusion: According to the current research, women with PCOS who have elevated levels of suPAR are also more likely to have hyperandrogenism and insulin resistance, which are risk factors for metabolic issues, endothelium and fibroblast dysfunction, and PCOS. This study addresses the connection between PCOS and SHBG, as well as related alterations in hormones and suPAR.Further research is required to fully understand the association between suPAR level and PCOS in the future.

KEWORDS: SuPAP, PCOS, ; insulin sensitivity; HOMA-IR and lipid profile .

1.INTRODUCTION

Polycystic ovarian syndrome is a common endocrine condition that affects up to 15% of women who are of reproductive age. Notably, a noteworthy association has been observed in recent decades between an increased frequency of PCOS and the rising incidence of obesity. Despite PCOS's high incidence and high cost, the condition's cause is still unknown[1]. The most prevalent endocrinopathy among fertile women is PCOS. It is a complicated, multidimensional illness. Chronic anovulation, an excess of testosterone, and a changed cardiometabolic profile are its distinguishing characteristics. Women with PCOS are more likely to have insulin resistance (IR), hyperinsulinemia, central obesity, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus (T2DM) as compared to women without PCOS who are matched for age and body mass index (BMI). Adipose tissue (AT) physiology impairment has been linked to PCOS.Adipocyte hypertrophy in PCOS appears to be caused by a combination of hyperandrogenemia and hyperinsulinemia. Adipose tissue produces adipocytes, which exude proinflammatory chemicals called adipokines in response to variations in adipocyte activity. These compounds increase sensitivity to low-grade inflammation[2].

Diabetes mellitus, obesity, dyslipidaemia, hypertension, anxiety, and depression are more common in women with PCOS. Health issues affect women with PCOS at every stage of life, including the years after menopause and before conception.The circle depicts the life cycle of a woman with PCOS[3]. If you have oligomenorrhea (65–87% had demonstrable polycystic ovaries on ultrasound), hirsutism (60–92%), acne (83%), or acne (45% in women with acne as a sole symptom), the typical ultrasound features of the polycystic ovary are easily the most common detectable sign associated with any of the typical symptoms. The inclusion of an ultrasound scan as a cornerstone of the diagnostic process is becoming increasingly warranted due to the well-known heterogenicity, unexpected character, and consistency in the clinical and endocrinological components of the condition, particularly in the reproductive age group[4]. The existence of 12 follicles or more in ovaries with a diameter of between 2 and 9 mm, or an increase in ovarian volume of more than 10 cm3 in one ovary at least, were the criteria for using ultrasound to detect polycystic ovarian alterations. This "string of pearls"-like arrangement of follicles along the ovary's border is one of the basic characteristics of PCOS ultrasonography[5]. Numerous

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studies have shown that individuals with PCOS have increased levels of antral and pre-antral follicle cells. Additionally, an overly high number of produced follicles is caused by the defective apoptotic activity of mature follicular cells. This abnormal development is further linked to the presence of ovarian cysts in the patients[6,7] . When uPAR is broken down and released from cells in response to inflammation, soluble uPAR, or suPAR, is created. SuPAR in type 2 diabetes is regarded as a pro-inflammatory signal. Concern with suPAR as a possible risk factor for T2DM, CVD, cancer, and general mortality has grown recently.Elevated serum suPAR levels have also been linked to cardiovascular problems and subclinical organ damage, which helps predict the causes of mortality in ischaemic stroke [8].

The bioactive form of the membrane-bound glycoprotein uPAR, known as soluble urokinase plasminogen activator receptor (suPAR), is mostly expressed on the surface of immune-active cells. Known by other names, including urokinase and vitronectin, the urokinase plasminogen activator receptor (uPAR) is expressed on fibroblasts, endothelial cells, megakaryocytes, keratinocytes, and some cancer cells. Additionally, immunological cells like neutrophils, macrophages, endothelial cells, activated T lymphocytes, and vascular smooth muscle cells display it on their surfac [9] In 1990, Danish researchers made the initial discovery of it as a biomarker linked to the start of cancer. Subsequent research into its potential as a sepsis biomarker was made possible by its association with the prognoses of patients with bacterial and other infections. Elevated levels of suPAR have been linked to an increased risk of death and severity of illness in a number of immunological conditions because inflammation raises the expression of both uPAR and suPAR[10].

2.MATERIAL AND METHODS

Ninety women between the ages of twenty and forty who had received a PCOS diagnosis within the last year were included in this case-control research using the Rotterdam ESHRE/ASRM 2003 criteria. The study was carried out at the AL-Zahra teaching hospital for obstetrics and gynaecology as well as the fertility clinic at AL-Sader Medical City in Najaf, Iraq, between December 2023 and March 2024.

Ninety volunteer women without PCOS who appeared healthy were compared to an age-matched control group of women with PCOS.The study was approved by the Najaf Health Directorate of the Hospital Administration for Obstetrics and Gynaecology and the Ethics Committee of the University of Kufa's Faculty of Science.Every individual signed an informed consent form. Patients with any form of chronic illness, including smokers, those with decreased ovarian reserve, those with type 1 and type 2 diabetes, people with hypertension, dyslipidaemia, hypertension, Cushing's syndrome, thyroid issues, cardiovascular illnesses, androgen-secreting tumours, and enzyme abnormalities (particularly in 21-hydroxylase). An anthropometric measurement known as body mass index (BMI) is calculated by dividing weight (kg) by height (m2). On cycle day 2, between 8 and 9 a.m., five millilitre samples of venous blood were taken following a 12-hour fast. After that, the serum was divided and stored at -20°C until analysis was completed.

Using colorimetric techniques and commercial test kits, serum glucose (FSG) and lipid profile (total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels) were assessed during the fasting examination. The amount of serum free testosterone was determined using ELISA kits (Monobind, USA). Sex hormone binding

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globulin (SHBG), fasting insulin (FINS), and other biomarkers were measured using ELISAkits (ELabscience/USA), and suPAR. Total testosterone (TT), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured using the immune-fluorescence method (Minividas, Biomerieux, France). Insulin resistance was calculated using the homeostatic model assessment (HOMA-IR), which was derived using a typical computation as follows. Weir and Jan (2019) state that the formula for calculating HOMA-IR is fasting insulin (IU/L) + fasting glucose (mmol/L) /22.5, with a cutoff value of > 2.5.In addition, the free androgens index (FAI) was calculated using the traditional technique FAI = total testosterone (TT)/SHBG × 100[11].

3. STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) software (version 25.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Each result's mean and standard deviation were noted. The statistical significance of the study's groups was ascertained using an unpaired student t-test, and t-tests were used to compare two independent samples. The link between variables was examined using Pearson's correlation analysis for the comparison of parameters among women affected by PCOS. The definition of statistical significance was a P-value of 0.05[12].

Ethical approval

The project received ethical approval from Kufa University's Kufa College of Science (license number 4000 on January 28, 2024). After each patient was told about the nature and objectives of the study, participants underwent a medical examination by a specialised physician to check for any indications or symptoms of PCOS. Patients' and employees' consent was gathered from private laboratories and the Al-Sadr Teaching Hospital, Al-Hakeem Hospital, and Al-Zahraa Hospital in the Governorate of Najaf.

4. RESULTS and DISCUSSION

4.1 Demographic Characteristics of Patients and Control groups

Table 4-1 displays the study groups' baseline characteristics. Ninety people with PCOS made up the 180 samples; ninety seemingly healthy women served as the control group. There is no discernible variation in the age variables between the groups under study. WHR and BMI were considerably greater in the patient group compared to the control group.

Table 4-1: **General Characteristics of the patients and control**

Variables	Groups		
	PCOS Patients group Mean±SD	Healthy group Mean±SD	P-value
No.(%)	90	90	-
Age(Years)	30.21± 5.67	30.34± 7.16	0.325

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BMI(kg/m²) **BMI:18.9-24.9** **BMI:25-29.9** **BMI:≥30**	29.66 ± 1.19 10(12%) 35.(38%) 45(50%)	23.62 ± 1.04 90(100%) - -	0.002
WHR	1.08± 0.06	0.74± 0.05	0.001
With Hirsutism	54(60%)	-	-
Without Hirsutism	36(40%)	-	-
Primary infertility	60(67%)	-	-
Secondary infertility	30(33%)	-	-
Irregular cycle	68(76%)	-	-
Regular cycle	22(24%)	-	-

The findings indicate that there is no statistically significant difference ($p>0.05$) in age or marital status between women with PCOS and the control group. The current study's findings concurred with those of another study [13]. The majority of the women with polycystic ovary syndrome were over the age of 25, and all patient groups ranged in age from 16 to 35. These findings are in line with the findings of Liang et al., who found that extreme obesity in the majority of 20–24, 25–29, and 32–41 year old PCOS women served as a trigger for doctors to consider PCOS diagnosis [14]. Obesity is frequent among PCOS-afflicted women in Iraq. Obesity is a risk factor that increases the effects of PCOS. It raises the possibility of metabolic problems. The existence of fat exacerbates insulin resistance. These women vary in their prevalence of obesity; many PCOS patients have normal BMIs. It is not necessary to be obese to diagnose PCOS[15]. Researchers view PCOS syndrome as one of the primary reasons of obesity and infertility. It has several aspects, including social and environmental factors in addition to genetic ones. Elevated blood levels of androgens, especially testosterone, are linked to PCOS on a regular basis. Acne and hirsutism—excessive facial and body hair—may follow from this [16]. Furthermore, very few research have specifically looked at the effects of the postwar inspection on sterility. The failure of females in different behaviours could have been attributed to a variety of parasites. Variations in the ovarian post-inflammatory (PI) surrounding the duct and Pretorian membrane were present in around 35% of women with sterility-agonized ovarian dysfunction (OD)[17] , Compared to the irregularly menstruation group, the regularly menstrual group was substantially older, had a higher basal FSH concentration, and had lower androgen levels [18].

Polycystic ovarian syndrome (PCOS) is characterised by long and irregular menstrual cycles, which have been linked to higher levels of androgen and lower levels of sex hormone binding globulin. Through in-person interviews, data on menstrual cycle irregularity, duration, and PCOS were gathered. The odds ratios (OR) and 95% confidence intervals (CIs) for ovarian cancer were determined using unconditional logistic regression models[19,20].

4.2 Serum SuPAR level in PCOS patients and healthy control group

The study groups' SuPAR levels were compared, as shown in Tables (4.2) and Figure (4.1). The outcome shows that, in comparison to the healthy control group, the SuPAR level was considerably

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higher **(P <0.0001)** in the PCOS patient groups.

Table (4.2): suPAR levels in the patient and healthy PCOS control groups

Parameter	Patient Group Mean ± SD	Healthy Group Mean ±SD	P-Value
suPAR (ng/mL)	2.0745±0.4102	1.0442±0.3894	<0.0001

The data represented as mean ± SD, SD: standard deviation, suPAR : Soluble urokinase plasminogen activator receptor

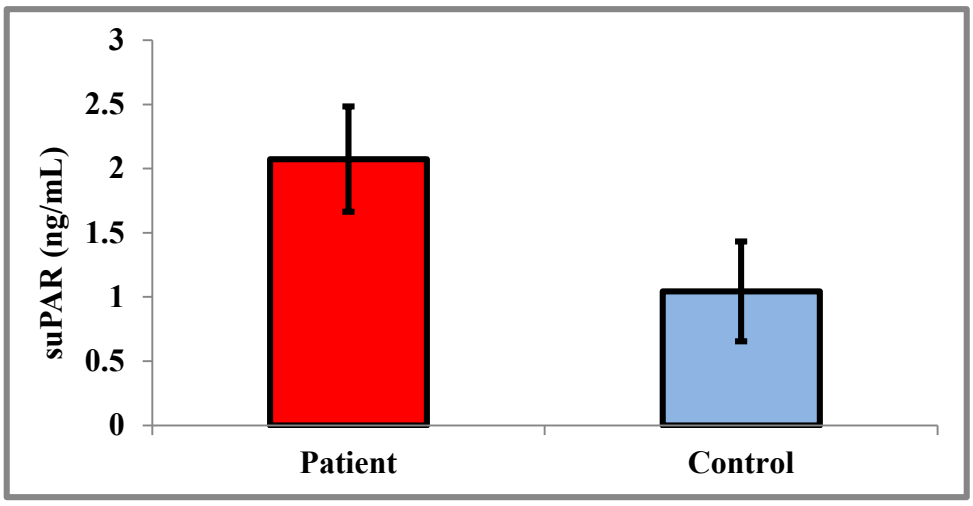

Figure (4.1): comparision in mean levels of SuPAR between PCOS patients with healthy control group.

Serum suPAR levels were considerably lower in the PCOS patients in this study (P = 0.0001). The plasma suPAR level and the serum LH level had a positive connection (P = 0.0001). Through the use of receiver operating characteristic analysis, as shown in tuble (3-4) and figure (4-2)1.775 was shown to be the PCOS cut-off value for suPAR9. A significant correlation between suPAR (OR [95% CI] [0.9, 1.000], P < 0.0001) and hormonal and metabolic changes in PCOS

4.2 Correlation analysis between serum suPAR levels with other Anthropometric and biochemical Parameters in women with PCOS Group.

Table (4.4) examines how the correlation coefficient assesses the impact of serum suPAR levels on biochemical indicators in women patients with PCOS. However, there was a significant positive association found between age, SHBG, and FT and suPAR levels.Significantly negative correlations have been seen between the serum levels of suPAR in the patient group and BMI, WHRM, LH,FSH, LH/FSH, TT, FIA, FSG, FIN, HOMA-IR, HOMA-%β, TG, and IL-39.

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Table 4-4 data of correlation between serum suPAR levels with clinical parameters in patients group

Parameters	r	p.value
Age (year)	0.297	0.049
BMI (kg/m^2)	0.305	0.006
WHR	0.350	0.001
LH (IU/L)	0.119	0.482
FSH (IU/L)	-0.147	0.650
LH/FSH	0.164	0.452
SHBG (pg/mL)	-0.289	0.053
TT (ng/mL)	0.228	0.071
FT (pg/mL)	0.285	0.052
FIA	0.178	0.382
FSG (mg/dL)	0.245	0.061
FIN (mIU/L)	0.297	0.048
HOMA - IR	0.342	0.001
HOMA-%β	-0.346	0.001
TC (mmoL/L)	0.211	0.073
TG (mmoL/L)	0.253	0.060
HDL-C (mmoL/L)	-0.168	0.138
LDL-C (mmoL/L)	0.023	0.842
VLDL-C (mmoL/L)	0.117	0.311
IL-39 (/mL)	-0.324	0.001
CTRP9 (ngLmL)	0.290	0.05
CD74 (ngLmL)	0.282	0.057

r: correlation coefficient , WHR: Waist-to-hip ratio, BMI: Body mass index, FSG: fasting serum glucose , , HOMA-IR: Homeostatic Model Assessment for Insulin Resistance , Quicki: quantitative insulin sensitivity check index ,FIN: fasting insulin, LH: luteinizing hormone , FSH: follicle stimulating hormone, TT: total testosterone , FT: free testosterone, FAI:free androgen index, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein -cholesterol, LDL-C : low-density lipoprotein- cholesterol , IL-39: Interleukin 39 , CTRP9: C1q/tumour necrosis factor-related protein-9 , CD74: Cluster of Differentiation 74 .

Although elevated LH is frequently seen, PCOS, or polycystic ovarian syndrome, cannot always be diagnosed with it. LH is known to trigger luteinisation, ovulation, and increased ovarian androgen production. Thus, it is among the main causes of hyperandrogenism in PCOS patients.In ovarian theca cells that have LH receptors, the primary inducer of androgen production is luteinizing hormone[21].

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Severe PCOS cases seem to be associated with higher LH concentrations. There has previously been evidence of a favourable association between folliculle count and ovarian volume. In addition, more severe cycle disruptions and a higher risk of infertility have been linked to PCOS patients with elevated LH levels. The degree of PCOS in female patients is also indicated by their hypersecretion of LH[22].

On the other hand, follicular development is impaired by a relative FSH deficiency [23]. A higher frequency of the LH pulse inhibits the synthesis of FSH and oestrogen, which stops the development of follicles and ovulation. In the end, this causes polycystic ovaries in PCOS patients[24].

One neuroendocrine characteristic of PCOS is hypothesised to be the consistently fast (GnRH) pulsatility that promotes pituitary LH over FSH synthesis and results in elevated LH concentrations and altered LH / FSH ratios that are diagnostic of the disorder. Low amounts of FSH prevent follicular expansion, while high levels of LH increase the production of ovarian androgen[25]. FSH hormones are produced by the pituitary and hypothalamus, which results in variations in these hormone levels in women who are impacted. The Rotterdam consensus states that in order to identify hyperandrogenism in women with PCOS, circulating free testosterone, or FAI measurements, should be employed rather than serum total testosterone [26,27].

There are several possible reasons why PCOS may result in increased prolactin release. the activity of oestrogens, which boost prolactin synthesis and secretion as well as the proliferation of lactotropic pituitary cells. In PCOS, elevated oestrogen levels may lead to an increase in prolactin concentrations[28].

It is commonly recognised that prolactin stimulates the release of more insulin from islets. Research indicates that prolactin may affect vital enzymes and transporters in the target organs involved in lipid and glucose metabolism as well as the balance of metabolism[29]. Thus, a close association between prolactin and thromboembolic stroke, insulin resistance, hypertension, and coronary syndrome has been hypothesised. Polycystic ovarian syndrome (PCOS) and hyperprolactinemia are two of the most prevalent causes of infertility in women[30].

Higher blood testosterone levels are closely correlated with higher serum LH levels [31]. The findings of this investigation and Chakrabarti, J. (2013) show a positive correlation between the two groups' age, WHR, BMI, and serum PCOS levels. The PCOS population was shown to have higher mean BMI, LH, and LH:FSH ratios. Women with PCOS also had significantly higher levels of androgens and insulin fasting. [32].

The study's PCOS participants had increased blood and ovarian levels of testosterone. A low-grade chronic inflammatory disease called PCOS may be connected to women's hyperandrogenism. Follic cells, endothelial cells, and adipocytes produce SuPAR, which may be impacted by PCOS-related metabolic issues.

The results of this study provide credence to the theory that hyperandrogenism could lead to a rise in suPAR synthesis. To ascertain the processes behind androgen-induced higher suPAR synthesis and if elevated circulating suPAR is an indication of the severity of innate immunity or a compensatory approach for hyperandrogenism, more research is required[33].

The current study discovered that hyperandrogenism and PCOS were both significant predictors of raised suPAR levels in women with PCOS, who also had considerably elevated suPAR levels.This study further emphasises the possible link between reproductive-age females' SHBG levels and PCOS risk.

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This meta-analysis evaluated publications that have been published up to this point in order to determine the effect size for SHBG levels[35] . Low serum SHBG plays a significant role in the pathophysiology of PCOS and is linked to its consequences and long-term prognosis. [35,36].

Receiver operating characteristic (ROC)

Table (4.3): Receiver operating characteristic-area under curve analysis of the measured biomarkers for the diagnosis of PCOS

Variables	Cut-off concentration	Sensitivity %	Specificity %	AUC	95% CI of AUC	p-value
suPAR (ng/mL)	1.775	91.3	91.1	97.1	0.94-1.000	<0.0001

AUC: Area Under the Curve, CI: Confidence Interval.

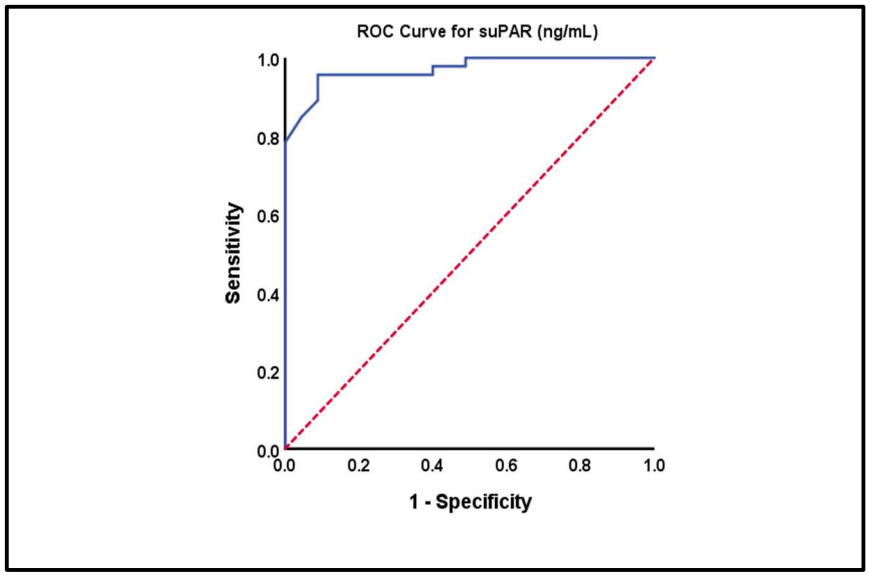

Figure 3-5: ROC curve of serum suPAR levels as discriminators of PCOS patients.

5. CONCLUSTION

Patients who are at risk of injury early on are identified by predictive biomarkers, requiring individualised treatment plans and continuous monitoring. All things considered, the serum of suPAR can be used as a useful biomarker for patient stratification and for identifying PCOS patients who may have endothelial dysfunction.SHBG has a major impact on the pathophysiology of PCOS and is linked to the difficulties and long-term prognosis of the condition. The link between SHBG and PCOS, along with related suPAR and hormone levels, are covered in this study.Further research is required to fully understand the association between suPAR and PCOS in the future.Not all PCOS instances exhibit the

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negative linear association between SHBG and the HOMA index and blood insulin level.

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