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The relationship between polycystic ovary syndrome phenotypes and systemic immune inflammation indices

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ABSTRACT

Aims: Polycystic ovary syndrome (PCOS) displays chronic, low-grade inflammation characterized by an enhanced release of pro-inflammatory cytokines. However, the extent of systemic inflammation and its variations across different PCOS phenotypes has not been sufficiently characterized. The study aimed to investigate the relationship between the presence and phenotypes of PCOS and systemic immune inflammation (SII) and response (SIRI) indices.

Methods: A total of 310 newly diagnosed PCOS patients and 105 healthy premenopausal women were included in this retrospective study. PCOS were categorized into four distinct phenotypes: phenotype A [hyperandrogenism (HA), oligomenorrhea (OA), and polycystic ovaries (PCO)], phenotype B (HA and OA), phenotype C (HA and PCO), and phenotype D (OA and PCO).

Results: Median SII and SIRI were higher in patients with PCOS than control group. The androgenic phenotypes group, specifically Phenotype A, exhibited elevated levels of SII and SIRI compared to the non-androgenic phenotype group. There was a positive correlation between these indices and hormonal parameters and insulin resistance. These relationships were particularly pronounced in the phenotype A group. Increased SIRI was an independent predictor of PCOS fold (OR=1.08, p<0.001). In distinguishing the androgenic phenotypes from the non-androgenic phenotypes, the threshold value of the SIRI was found to be >1.1 with 67.1% sensitivity and 81.2% specificity. It was incapable of distinguishing phenotype B from Phenotype C, but it was found successful in predicting phenotype A among all phenotypes.

Conclusion: Elevated SII and SIRI levels were associated with the presence of PCOS and its phenotypes, particularly phenotype A. SIRI demonstrated potential as a screening tool for phenotypic discrimination of PCOS, beyond predicting its presence.

Keywords: Polycystic ovary syndrome, systemic immune inflammation, systemic immune inflammation index, phenotype, insulin resistance

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder that affects women of reproductive age, and its estimated prevalence ranges from 4% to 20% worldwide.[1] PCOS is characterized by the presence of chronic oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology.[2] While the exact pathogenesis of PCOS remains unclear, there is evidence suggesting the involvement of low-grade chronic inflammation, insulin resistance (IR), as well as various genetic and environmental factors.[3] These factors may predispose individuals with PCOS to a variety of unfavorable health outcomes, including metabolic syndrome, cardiovascular diseases, pregnancy complications, and gynecological cancer.[4] Hence, there is a need for further investigation and understanding of the effects of these potential mechanisms.

Human preovulatory follicles have been observed to contain a substantial number of immunocompetent cells, including macrophages, T-cells, and B-cells.[5] It has also been demonstrated that women with PCOS have a chronic low-grade inflammation marked by increased release of pro-inflammatory cytokines such as interferons and interleukins.[6] Furthermore, low-grade inflammation is thought to be a precursor to IR, which is also linked to the development of PCOS.[7,8] These findings indicate a potential link between immune function

and PCOS. However, the extent of systemic inflammation and its variations across different PCOS phenotypes has not been sufficiently characterized.

Considering the potential contribution of low-grade inflammation to the development of PCOS, we postulated an association between PCOS phenotypes and systemic immune inflammation indices derived from leukocytes, which play a role in the production of pro-inflammatory cytokines. Among these indices, we evaluated the systemic immune inflammation index (SII) and systemic inflammation response index (SIRI), which have not yet been investigated in the context of PCOS but are claimed to be associated with metabolic syndrome and cardiovascular diseases.[9,10] The SII, which is an indicator of inflammatory status, is calculated by platelet count×neutrophil count/lymphocyte count, while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count×monocyte count/lymphocyte count.[11,12]

In the present study, we aimed to investigate the relationship between the presence and phenotypes of PCOS and SII and SIRI indices. To gain further insight into the relationship of systemic immune inflammation on PCOS phenotypes, we evaluated the association between these indices, hormonal parameters, and IR across phenotypes.

METHODS

This retrospective study conducted at Bakırköy Sadi Konuk Hospital Gynecology and Obstetrics Clinic from June 2015 and June 2020. The study was conducted with the permission of the Clinical Researches Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 12.09.2022, Decision No: 146/19) and was conducted in compliance with the relevant ethical guidelines and the Declaration of Helsinki (2013 Brazil revision). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study Population

A total of 642 woman diagnosed with PCOS who visited the Outpatient Clinic during the study period were evaluated retrospectively. The diagnosis of PCOS was made based on the on the agreed ASRM/ESHRE criteria adopted in Rotterdam, which required the presence of at least two out of the following three criteria: (1) oligo-ovulation and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries observed via ultrasound. The diagnosis of PCOS was confirmed after excluding other potential causes of hyperandrogenemia or ovulation dysfunction, such as thyroid disease, congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, 21-hydroxylase deficiency, and hyperprolactinemia.[2] The inclusion criteria in this study were as follows: age between 18 and 40 years old, newly diagnosis of PCOS, fertility requirements within the past year. The following exclusion criteria were then also applied: a history of PCOS or PCOS-related treatment, any systemic inflammatory or autoimmune diseases, history of hypertension or diabetes mellitus, history of coronary artery diseases, liver diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid drugs, hormone therapy, early menopause, pregnancy, lactation, use of smoke and alcohol, and missing clinical data. After this exclusion process, 310 patients who had newly diagnosed PCOS were enrolled in this study.

Additionally, the study included a control group consisting of 105 healthy premenopausal women from the general community who met the specific inclusion criteria: (1) consistent regularity in menstrual cycles, (2) absence of observable clinical indications of hyperandrogenemia, including acne, hirsutism, seborrhea or alopecia, and (3) confirmation of normal ovarian morphology as determined through transvaginal ultrasound examination.

Study Protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. In accordance with the Rotterdam criteria, the ultrasonographic diagnosis of PCOS necessitates the observation of 12 or more ovarian follicles with a diameter ranging from 2 to 9 mm, and/or a discernible increase in ovarian volume exceeding 10 mL. Regarding the diagnosis of PCOS, the fulfillment of these criteria by at least one ovary has been accepted satisfactory.[2] In accordance with the Rotterdam criteria, women diagnosed with PCOS were categorized into four distinct phenotypes: phenotype A [hyperandrogenism (HA), oligomenorrhea (OA), and polycystic ovaries (PCO)], phenotype B (HA and OA), phenotype C (HA and PCO), and phenotype D (OA and PCO).

Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations on days 2 to 5 of the menstrual cycle after a 12-hour fasting period then analyzed in a single laboratory using the same methodology as described below.

Laboratory Parameters

A Beckman DxC device (Beckman Diagnostic Corp., CA, ABD) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., IN, USA) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), leukocyte count (impedance method), triglycerides and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[13] Follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), total testosterone (TT), Anti-mullerian hormone (AMH), and fasting insulin levels were determined using the chemiluminescent microparticle immunoassay method (Abbott Architect i2000).

The LH/FSH ratio (LFR) was obtained by dividing the LH by the FSH. Homeostatic Model Assessment for IR (HOMA-IR) was calculated using the following formula: HOMA-IR=[fasting insulin (mU/mL)xfasting glucose (mg/dL)/405]. The inflammation indices were respectively calculated as follows: NLR=neutrophil count/lymphocyte count; PLR=platelet count/lymphocyte count; SII=platelet count×neutrophil count/lymphocyte count; SIRI=neutrophil count×monocyte count/lymphocyte count;[11,12] and MHR=monocyte count/HDL-C.

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data

determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values while non-normally distributed variables are given as median (25th-75th quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test or ANOVA test (post-hoc: Bonferroni test) and Kruskall Wallis-H test (post-hoc: Dunn's test) were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of PCOS. The components of LFR, HOMA-IR, SII, SIRI and MHR were not included in the multivariable regression model because of their multi-collinearity. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Significance was accepted at P<0.05 (*) for all statistical analyses.

RESULTS

The PCOS population included 310 patients with a mean age of 28.2±5.5 years and these patients were mostly phenotype A. The characteristic findings of PCOS patients at the time of diagnosis are presented in **Supplementary Table 1**. The levels of LFR, DHEA-S, TT and AMH were higher in the PCOS group compared to control group. The median HOMA-IR level (2.7 vs. 1.6, p<0.001), median SII level (537.6 *vs.* 354.8, p<0.001) and median SIRI level (1.1 vs. 0.4, p<0.001) were higher in the PCOS group than control group (**Supplementary Table 1**).

Demographic findings did not differ significantly according to phenotypes of PCOS. The levels of LFR, DHEA-S, TT and AMH exhibited variations in all PCOS phenotypes when compared to the control group. While the median LFR and mean DHEA-S levels were similar in the hyperandrogenic phenotypes groups, they were higher than the non-hyperandrogenic phenotype group. While The median TT and median AMH levels were higher in the phenotype A group compared to the other PCOS phenotypes groups whereas they exhibited similar levels in the phenotype B, C, and D groups. The median HOMA-IR level was similar in the phenotype A and B groups but it was higher compared to the other PCOS phenotypes groups. The levels of SII and SIRI were higher in all PCOS phenotype groups compared to the control group. The median SII and SIRI levels were higher in phenotype A, comparable in phenotypes B and C, and lower in phenotype D (**Table 1**).

SII and SIRI were positively correlated with levels of LFR, DHEA-S, TT, AMH, and HOMA-IR (**Supplementary Table 2**). This association was more pronounced in the phenotype A group (**Table 2**).

Among the potential confounding factors associated with PCOS (**Supplementary Table 1**), LFR, DHEA-S, TT, AMH, HOMA-IR, SII, SIRI, MHR and CRP were included in the multivariable logistic regression model. Increased LFR, increased AMH, increased HOMA-IR, and increased SIRI were determined as independent predictors of PCOS. Accordingly, a 1% increase in SIRI increased the risk of PCOS by 1.08-fold

Table 1 (Supplementary). Demographic and clinical findings of PCOS patients

Variables	Control n=105	PCOS n=310	p-value
Demographic findings			
Age, years	27.6±6.4	28.2±5.5	0.355
BMI, kg/m^2	25.8±3.4	26.2±3.1	0.266
WHR	0.7±0.2	0.7±0.2	0.624
Hormonal findings			
LH, mIU/ml	6.4 (5.3-8.0)	8.1 (6.6-10.1)	<0.001*
FSH, mIU/ml	7.5±1.7	6.2±1.8	<0.001*
LFR	0.8 (0.6-0.9)	1.4 (1.1-1.9)	<0.001*
DHEA-S, µg/dl	210.8±53.2	276.8±95.1	<0.001*
TT, ng/ml	0.2 (0.1-0.3)	0.4 (0.3-0.6)	<0.001*
AMH, ng/ml	2.8 (1.9-3.7)	7.0 (5.1-9.8)	<0.001*
Biochemical findings			
Glucose, mg/dl	88.5±6.8	90.1±9.1	0.162
Insulin, µU/ml	7.7 (5.1-10.9)	11.4 (8.3-14.3)	<0.001*
HOMA-IR	1.6 (1.0-2.3)	2.7 (2.0-3.7)	<0.001*
Leukocytes,×10^9/L	6.6±1.7	8.1±2.4	<0.001*
Neutrophils,×10^9/L	3.6±1.1	5.2±1.6	<0.001*
Lymphocytes,×10^9/L	2.5±0.7	2.3±0.7	0.045*
Monocytes,×10^9/L	0.3±0.1	0.6±0.2	<0.001*
Platelets,×10^9/L	242.6±50.0	255.2±52.1	0.032*
NLR	0.5±0.1	0.7±0.2	<0.001*
PLR	103.9±30.1	129.1±33.8	<0.001*
SII	354.8 (270.3-440.4)	537.6 (442.6-690.7)	<0.001*
SIRI	0.4 (0.3-0.7)	1.1 (0.8-1.5)	<0.001*
Cholesterol, mg/dl	180.7±53.8	184.0±48.4	0.765
LDL-C, mg/dl	106.7±41.5	107.1±37.0	0.914
HDL-C, mg/dl	68.0±20.4	55.9±15.7	0.014*
Triglyceride, mg/dl	87.0 (62.0-123.0)	94.5 (68.0-136.0)	0.083
MHR	6.2 (4.7-8)	9.5 (7.2-13.1)	<0.001*
CRP, mg/L	0.3 (0.1-0.9)	1.3 (0.5-2.5)	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone, WHR: Waist to hip ratio

Table 1. Comparison of demographic and clinical findings by phenotype of PCOS

Variables	Control n=105	Phenotype A n=102	Phenotype B n=66	Phenotype C n=63	Phenotype D n=79	p-value
Demographic findings						
Age, years	27.6±6.4	28.4±4.8	27.9±4.3	28.1±4.5	28.4±4.5	0.550
BMI, kg/m²	25.8±3.4	26.0±3.2	26.4±2.0	26.5±1.8	26.2±2.5	0.197
WHR	0.7±0.2	0.8±0.1	0.7±0.2	0.8±0.1	0.7±0.2	0.562
Hormonal findings						
LH, mIU/ml	**6.4 (5.3-8.0)**	8.9 (6.8-11.7)	9.1 (7.1-10.3)	8.7 (7.1-10.2)	**7.8 (6.5-9.4)**	<0.001*
FSH, mIU/ml	**7.5±1.7**	6.1±1.7	6.0±1.5	6.2±1.7	**6.8±1.8**	<0.001*
LFR	**0.8 (0.6-0.9)**	1.6 (1.2-2.1)	1.4 (1.1-2.0)	1.4 (1.0-2.1)	**1.1 (0.8-1.7)**	<0.001*
DHEA-S, µg/dl	**210.8±53.2**	291.9±91.3	284.6±87.6	302.4±83.5	**232.6±67.0**	<0.001*
TT, ng/ml	**0.2 (0.1-0.3)**	**0.6 (0.4-0.8)**	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.4 (0.2-0.5)	<0.001*
AMH, ng/ml	**2.8 (1.9-3.7)**	**8.5 (6.0-10.9)**	6.0 (4.9-7.7)	6.6 (5.0-8.3)	6.9 (5.2-9.2)	<0.001*
Biochemical findings						
Glucose, mg/dl	88.5±6.8	91.1±8.7	90.5±8.3	89.4±9.8	88.6±9.1	0.387
Insulin, µU/ml	**7.7 (5.1-10.9)**	12.1 (9.5-16.3)	12.4 (9.8-15.4)	11.7 (8.2-14.1)	**8.9 (6.0-11.2)**	<0.001*
HOMA-IR	**1.6 (1.0-2.3)**	3.1 (2.3-4.5)	3.2 (2.5-4.7)	**2.6 (2.1-3.2)**	**1.9 (1.4-2.6)**	<0.001*
Leukocytes,×10⁹/L	6.6±1.7	8.8±2.5	8.0±2.1	8.3±2.2	6.6±2.0	<0.001*
Neutrophils,×10⁹/L	3.6±1.1	6.0±1.8	5.2±1.7	5.1±1.6	4.2±1.2	<0.001*
Lymphocytes,×10⁹/L	2.5±0.7	2.2±0.7	2.2±0.5	2.4±0.7	2.4±0.6	0.014*
Monocytes,×10⁹/L	0.3±0.1	0.6±0.2	0.5±0.2	0.6±0.1	0.5±0.1	<0.001*
Platelets,×10⁹/L	242.6±50.0	264.8±55.0	251.3±48.4	250.0±50.7	248.6±48.6	0.048*
NLR	0.5±0.1	0.7±0.1	0.7±0.2	0.6±0.1	0.7±0.2	<0.001*
PLR	103.9±30.1	137.4±32.1	133.4±34.1	122.4±26.4	120.4±27.0	<0.001*
SII	354.8 (270.3-440.4)	671.6 (531.0-823.7)	543.1 (457.8-655.8)	526.4 (442.1-628.4)	445.7 (379.0-525.1)	<0.001*
SIRI	0.4 (0.3-0.7)	1.7 (1.2-2.4)	1.2 (1.0-1.5)	1.1 (0.9-1.5)	0.8 (0.6-1.1)	<0.001*
Cholesterol, mg/dl	180.7±53.8	185.1±45.1	176.3±50.7	191.8±55.3	177.1±41.7	0.336
LDL-C, mg/dl	106.7±41.5	110.7±37.4	100.3±42.5	115.4±37.6	101.5±28.9	0.112
HDL-C, mg/dl	68.0±20.4	**53.1±14.4**	**51.0±15.0**	58.5±17.8	62.3±13.4	<0.001*
Triglyceride, mg/dl	87.0 (62.0-123.0)	89.0 (65.4-129.6)	96.3 (73.2-156.4)	97.3 (78.5-126.0)	87.6 (61.1-136.3)	0.165
MHR	**6.2 (4.7-8)**	10.7 (7.5-14.6)	10.2 (7.8-13.3)	**8.2 (7.3-11.1)**	**7.8 (6.2-9.6)**	<0.001*
CRP, mg/L	**0.3 (0.1-0.9)**	**2.0 (0.7-3.8)**	1.5 (0.5-3.3)	1.3 (0.5-2.5)	**0.8 (0.3-1.7)**	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone, WHR: Waist to hip ratio

Table 2 (Supplementary). Findings related to systemic immune inflammation indices in PCOS patients

Variables	SII		SIRI	
	r	p	r	p
Demographic findings				
Age	0.040	0.479	0.012	0.828
BMI	0.036	0.523	0.143	0.112
Hormonal findings				
LH	0.266	0.048*	0.287	0.030*
FSH	-0.214	0.143	-0.218	0.120
LFR	0.288	0.031*	0.336	<0.001*
DHEA-S	0.280	0.035*	0.327	<0.001*
TT	0.293	0.028*	0.315	<0.001*
AMH	0.284	0.033*	0.320	<0.001*
Biochemical findings				
Glucose	0.127	0.467	0.110	0.487
Insulin	0.263	0.048*	0.289	0.027*
HOMA-IR	0.306	<0.001*	0.337	<0.001*
NLR	0.565	<0.001*	0.446	<0.001*
PLR	0.386	<0.001*	0.186	0.480
SIRI	0.523	<0.001*	-	-
Cholesterol	0.139	0.491	0.103	0.663
LDL-C	0.102	0.669	0.119	0.545
HDL-C	-0.189	0.496	-0.196	0.452
Triglyceride	0.164	0.461	0.188	0.400
MHR	0.311	<0.001*	0.415	<0.001*
CRP	0.305	<0.001*	0.321	<0.001*

*: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, BMI: Body-mass index, CRP: C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HDL-C: High-density lipoprotein cholesterol, HOMA-IR: Homeostatic model of insulin resistance, LDL-C: Low-density lipoprotein cholesterol, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PCOS: Polycystic ovary syndrome, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, WHR: Waist to hip ratio

Table 2. The relationship between hormonal parameters, insulin resistance, and systemic immune inflammation indices based on phenotype of PCOS

	Variables	SII		SIRI	
		r	p	r	p
Phenotype A	LFR	0.364	<0.001*	0.389	<0.001*
	DHEA-S	0.321	<0.001*	0.366	<0.001*
	TT	0.315	<0.001*	0.341	<0.001*
	AMH	0.317	<0.001*	0.354	<0.001*
	HOMA-IR	0.322	<0.001*	0.381	<0.001*
Phenotype B	LFR	0.314	<0.001*	0.337	<0.001*
	DHEA-S	0.305	0.018*	0.320	0.004*
	TT	0.306	<0.001*	0.315	<0.001*
	AMH	0.291	0.025*	0.318	<0.001*
	HOMA-IR	0.310	<0.001*	0.342	<0.001*
Phenotype C	LFR	0.305	<0.001*	0.310	<0.001*
	DHEA-S	0.311	<0.001*	0.310	<0.001*
	TT	0.296	0.010*	0.309	0.001*
	AMH	0.278	0.046*	0.281	0.036*
	HOMA-IR	0.290	0.027*	0.317	<0.001*
Phenotype D	LFR	0.285	0.030*	0.290	0.027*
	DHEA-S	0.292	0.022*	0.283	0.032*
	TT	0.280	0.041*	0.289	0.026*
	AMH	0.283	0.044*	0.297	0.019*
	HOMA-IR	0.276	0.050*	0.288	0.029*

*: p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, DHEA-S: Dehydroepiandrosterone sulfate, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, TT: Total testosterone

(OR=1.08, p<0.001) (**Supplementary Table 3**). The threshold value of the SIRI was found to be >0.6 with 87.2% sensitivity and 74.8% specificity and it showed superior diagnostic performance compared to the other inflammation indices in predicting PCOS (**Supplementary Table 4**) (**Figure 1A**). When the diagnostic performance of SIRI compared to other independent predictors of PCOS, it was lower than AMH, and superior to LFR and HOMA-IR (**Figure 1B**).

In distinguishing the non-androgenic phenotypes of PCOS from the control group, the threshold value of the SIRI was found to be >0.6 with 92.4% sensitivity and 61.0% specificity (**Figure 2A**). In distinguishing the androgenic phenotypes from the non-androgenic phenotypes, the threshold value of the SIRI was found to be >1.1 with 67.1% sensitivity and 81.2% specificity (**Figure 2B**). SIRI showed superior diagnostic performance compared to SII in the phenotypic differentiation

Table 3 (Supplementary). Independent predictors of PCOS

Variables	Univariable regression				Multivariable regression			
	OR	95% CI		p-value	OR	95% CI		p-value
		Lower	Upper			Lower	Upper	
LFR, %	1.04	1.03	1.05	<0.001*	1.03	1.01	1.04	0.004*
DHEA-S	1.11	1.07	1.15	<0.001*	-	-	-	-
TT, $\times 10^2$	1.06	1.04	1.08	<0.001*	-	-	-	-
AMH	3.10	2.42	3.98	<0.001*	4.88	2.83	8.42	<0.001*
HOMA-IR	3.18	2.33	4.35	<0.001*	2.98	1.53	5.84	0.001*
SII	1.10	1.08	1.12	<0.001*	-	-	-	-
SIRI, $\times 10^2$	1.06	1.05	1.07	<0.001*	1.08	1.04	1.11	<0.001*
MHR	1.40	1.28	1.54	<0.001*	-	-	-	-
CRP	3.23	2.25	4.64	<0.001*	-	-	-	-
					Nagelkerke R^2 = 0.872; p< 0.001*			

The components of LH/FSH ratio, HOMA-IR, SII, SIRI and MHR were not included in the multivariable regression model because of their multi-collinearity. The effects of age, BMI, and waist to hip ratio were adjusted for multivariable regression analysis. * p-value <0.05 shows statistical significance. AMH: Anti-müllerian hormone, CI: Confidence interval; CRP; C-reactive protein, DHEA-S: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, HOMA-IR: Homeostatic model of insulin resistance, LH: Luteinizing hormone, LFR: LH to FSH ratio, MHR: Monocyte count to HDL-C ratio, OR: Odds ratio, PCOS: Polycystic ovary syndrome, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, TT: Total testosterone

Table 4 (Supplementary). The diagnostic performance of SII and SIRI compared to leukocyte-based inflammatory indices and other independent predictors of PCOS

Variables	AUC±SE	95% CI	Sensitivity	Specificity	Threshold value	p-value
SII	0.83±0.02	0.79-0.87	81.3%	72.4%	>421.2	<0.001
SIRI	0.89±0.02	0.86-0.92	87.2%	74.8%	>0.6	<0.001
NLR	0.78±0.02	0.74-0.83	81.0%	67.6%	>0.5	<0.001
PLR	0.72±0.03	0.58-0.66	77.1%	61.9%	>106.5	<0.001
MHR	0.78±0.03	0.74-0.82	75.8%	69.5%	>7.2	<0.001
LFR	0.83±0.02	0.79-0.87	82.6%	75.2%	>1.0	<0.001
AMH	0.94±0.02	0.91-0.96	84.2%	89.5%	>5.7	<0.001
HOMA-IR	0.79±0.03	0.75-0.83	77.4%	70.5%	>1.9	<0.001

AMH: Anti-müllerian hormone, AUC: Area under the curve, CI: Confidence interval, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

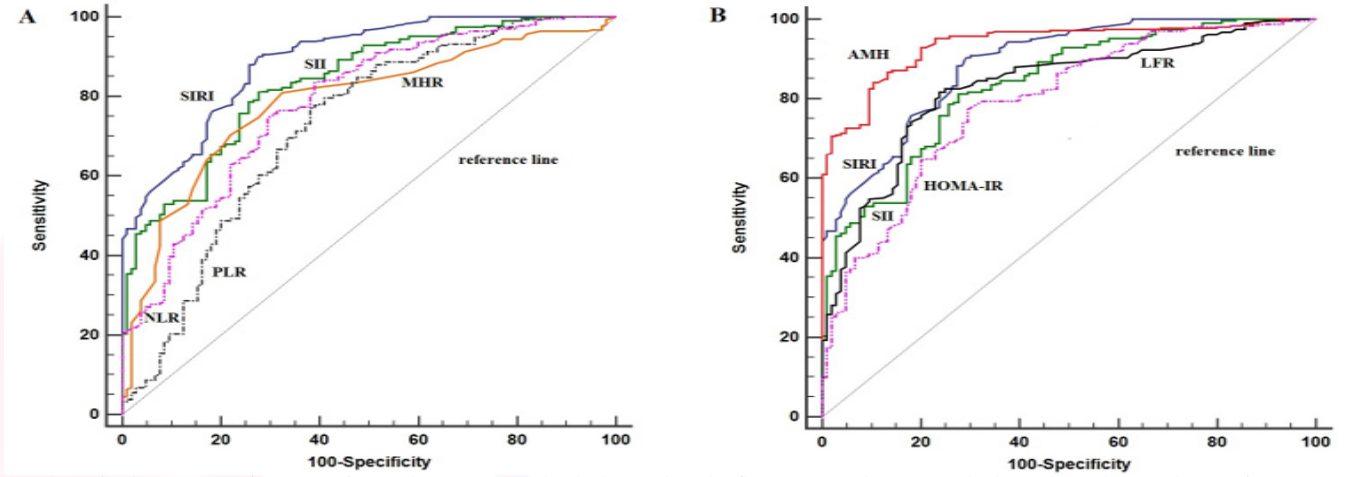

Figure 1. The diagnostic performance of SII and SIRI compared to leukocyte-based inflammatory indices (**A**) and other independent predictors of PCOS (**B**).
AMH: Anti-müllerian hormone, HOMA-IR: Homeostatic model of insulin resistance, LFR: Luteinizing hormone to follicle stimulating hormone ratio, MHR: Monocyte to HDL-C ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

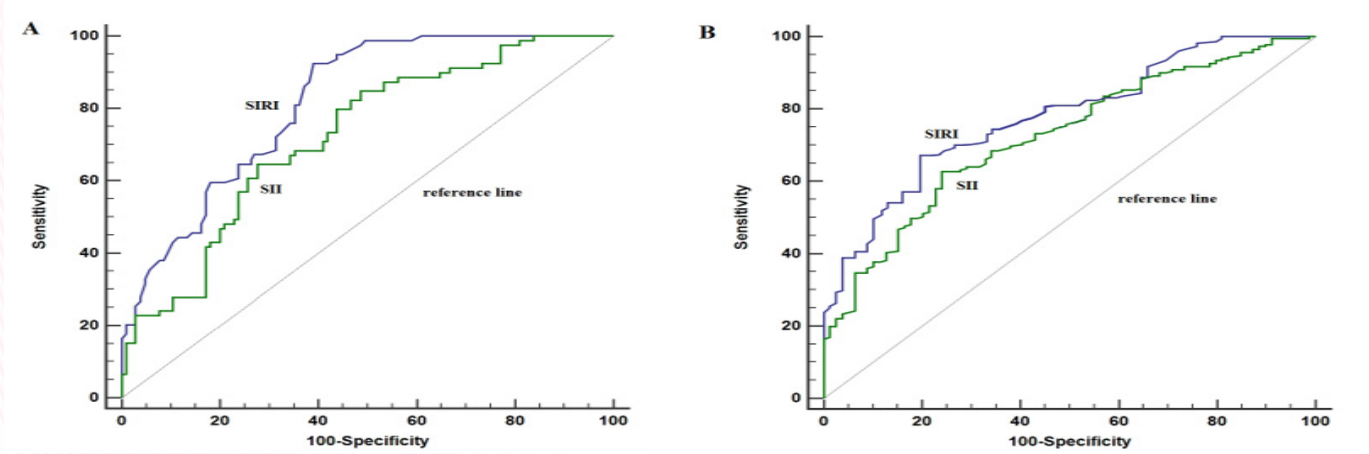

Figure 2. The diagnostic performance of SII and SIRI in distinguishing the non-androgenic phenotypes (vs. the control group) (**A**) and the androgenic phenotypes (vs. the non-androgenic phenotypes) (**B**)
SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index

of PCOS. The diagnostic performance of SII and SIRI in predicting PCOS phenotypes is shown in **Table 3**. Although SII and SIRI were incapable of distinguishing phenotype B from phenotype C, they were found successful in predicting phenotype A among all the phenotypes.

DISCUSSION

To our knowledge, this is the first study in the literature to report the association between the immune inflammation indices and the phenotypes of PCOS. The associations between PCOS and high SII and SIRI indices are not surprising, as previous limited studies found that increased levels of the NLR, PLR, or leukocyte components, as well as the MHR, were predictive of PCOS.[14,16] However, to obtain a more comprehensive assessment of immune inflammation in PCOS, it may be necessary to consider a broader range of immune cell subsets. While a few case-control studies have demonstrated elevated levels of SII in PCOS patients,[17,18] current findings suggest that SIRI may be a more significant indicator.

SIRI exhibited not only a more pronounced correlation with hormonal parameters but also served as an independent marker of PCOS. During the inflammatory process in PCOS, neutrophils, acting as the frontline immune defenders, initiate the induction of macrophages through the activation of the nuclear factor (NF)-κB pathway.[19] Macrophages secrete migration inhibitory factor (MIF), a pro-inflammatory cytokine, which triggers cytokinesis through the

Table 3. The diagnostic performance of SII and SIRI in distinguishing between phenotypes of PCOS

Variables	SII	SIRI
Phenotype D vs. control		
AUC±SE	0.72±0.04	0.82±0.03
95% CI	0.65-0.79	0.75-0.87
Sensitivity	64.6%	92.4%
Specificity	72.4%	61.0%
Threshold value	>421.2	>0.6
P-value	<0.001	<0.001
Phenotype C vs. phenotype D		
AUC±SE	0.67±0.05	0.72±0.04
95% CI	0.58-0.75	0.64-0.79
Sensitivity	71.4%	%75.7
Specificity	68.2%	%73.4
Threshold value	>480.6	>1.0
p-value	<0.001	<0.001
Phenotype B vs. phenotype C		
AUC±SE	0.50±0.05	0.52±0.04
95% CI	0.41-0.59	0.44-0.63
Sensitivity	56.3%	59.1%
Specificity	34.9%	30.2%
Threshold value	>530.9	>1.1
p-value	0.941	0.904
Phenotype A vs. phenotype B/C		
AUC±SE	0.66±0.04	0.72±0.04
95% CI	0.61-0.72	0.64-0.80
Sensitivity	69.6%	76.5%
Specificity	62.5%	70.2%
Threshold value	>586.3	>1.4
p-value	<0.001	<0.001

AUC: Area under the curve, CI: Confidence interval, SE: Standard error, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, vs: Versus

mitogen-activated protein kinase (MAPK) signaling pathway,[20] and MIF stimulates the NF-κB pathway, leading to increased levels of testosterone and LH.[21] Previous studies demonstrated that in the blood of women with PCOS, abnormal activation of T cells, the main component of lymphocytes, and macrophages leads to the production of cytokines such as and interferon (IFN)- alpha (α),- gamma (γ) and interleukin (IL) -2, -4, -5, -10.[6] Hence, immune system-initiated leukocyte activation may be a key player in the pathogenesis and phenotype of PCOS.

The present study findings revealed that hyperandrogenic phenotypes of PCOS, particularly phenotype A, have higher levels of SII and SIRI. Hormone levels can exert an influence on both the endocrine and immune systems, leading to variations in the inflammatory environment among different phenotypes of PCOS. An elevated androgen level in PCOS patients has been linked to a significant reduction in T cell count.[8] Lipid metabolism, which contributes to the differentiation of monocytes into macrophages, tends to be more impaired in hyperandrogenic phenotypes of PCOS compared to non-hyperandrogenic phenotype.[22] It has also been reported that the risk of metabolic dysfunction is higher in patients with the full-blown PCOS (phenotype A).[23] MHR levels were higher in phenotype A but lower in phenotype D, similar to the findings of a previous study.[24] On the other hand, pro-inflammatory cytokines produced by immune cells have the potential to stimulate androgen production, induce IR, and disrupt the secretion of the hypothalamic-pituitary-ovarian axis.[8] Thus, chronic inflammation and hyperinsulinemia can contribute to anovulation by affecting the hypothalamic-pituitary-ovarian axis and increasing the LFR.[25,26] Consistent with these mechanisms, phenotype A, which is associated with increased IR and greater severity of hyperandrogenism,[27] may exhibit a higher inflammatory milieu. In the phenotype A, correlations between systemic immune-inflammation indices, especially SIRI, and levels of LFR, AMH, androgen blood serum, and HOMA-IR were more pronounced.

To the best of our knowledge, this is the first study to compare the diagnostic performance of SII and SIRI with other leukocyte-based inflammatory indices and hormonal parameters for identifying PCOS patients. SIRI exhibited superior diagnostic performance compared to other parameters, with the exception of AMH. It has been reported that AMH levels, which serve as direct indicator of the follicular pool, are elevated in instances of oligo-anovulation and hyperandrogenism. This could elucidate the superior diagnostic performance exhibited by AMH.[28,29] On the other hand, it has been demonstrated that elevated cytokine release associated with PCOS can lead to a rise in AMH levels.[30] In clinical practice, the SII and SIRI indices, which can be easily obtained in a simple and cost-effective manner, may serve as valuable biomarkers for a more comprehensive evaluation of the inflammatory status in different PCOS phenotypes. This multifaceted approach could provide a more accurate representation of the immune-inflammatory processes involved in PCOS and potentially enhance the predictive power of such assessments. This hypothesis is strengthened by the identification of SII and SIRI as superior prognostic indicators compared to NLR and PLR in diverse cancer types.[31,32] Furthermore, these indices serve as significant indicators for the metabolic syndrome and cardiovascular diseases that patients with PCOS are predisposed to.[9,10] This study revealed that SIRI demonstrated superior diagnostic performance, as compared to SII, in distinguishing among various PCOS phenotypes. SIRI exhibited high sensitivity in distinguishing non-androgenic phenotypes compared to the control group, while demonstrating high specificity in differentiating these phenotypes from androgenic ones. Besides, SIRI has acceptable diagnostic performance in predicting phenotype A among androgenic phenotypes.

Limitations

This study is subject to several limitations. Firstly, its single-center retrospective design precludes the establishment of a cause-effect relationship. Another important limitation is that cytokines that play a role in the inflammatory response have not been analyzed. Finally, subtypes of lymphocytes and monocytes were not evaluated. These may provide a better understanding of the role of inflammation in the phenotypes of PCOS.

CONCLUSION

Each of the PCOS phenotypes had higher SII and SIRI levels compared to healthy controls. The androgenic phenotypes, specifically Phenotype A, exhibited elevated levels of SII and SIRI compared to the non-androgenic phenotype. Additionally, there was a positive correlation between SII and SIRI indices and IR and hormonal parameters. These relationships were particularly pronounced in the phenotype A of PCOS. Increased SIRI levels were an independent predictor of PCOS and it showed superior diagnostic performance compared to the other inflammation indices. Furthermore, SIRI had the potential to differentiate between phenotypes A and D of PCOS. Therefore, SIRI could potentially be a useful screening tool in the phenotypic discrimination of PCOS, beyond merely predicting the presence of the syndrome.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 12.09.2022, Decision No: 146/19).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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