

Study on the Association Between the Systemic Immune-Inflammation Index and Polycystic Ovary Syndrome in Women Undergoing in vitro Fertilization for Subfertility

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Purpose: Polycystic ovary syndrome (PCOS) is closely associated with chronic low-grade inflammation. Systemic immune-inflammation index (SII) based on complete blood cell count has shown superior discriminative value in a variety of diseases, but its role in PCOS is still unclear. This study aimed to investigate the association between SII and PCOS in women undergoing their first in vitro fertilization (IVF) treatment with a gonadotropin-releasing hormone (GnRH) antagonist protocol.

Materials and Methods: A total of 334 women undergoing their first IVF treatment with a GnRH antagonist protocol from January 2019 to December 2025 were included in this study. They were divided into the PCOS group (n=160) and the non-PCOS group (n=174). Demographic and physical indicators, reproductive endocrine indicators, systemic inflammatory indicators, infertility situation, ovulation induction treatment parameters, and trigger day indicators were collected. Binary logistic regression was used to identify the independent associated factors of PCOS.

Results: The results of the multivariate analysis indicated that anti-Mullerian hormone (AMH) ($OR=1.437$, 95% CI : 1.222–1.690, $P<0.001$), basal follicle-stimulating hormone (FSH) ($OR=0.718$, 95% CI : 0.519–0.993, $P=0.046$), luteinising hormone (LH) ($OR=1.293$, 95% CI : 1.100–1.519, $P=0.002$), testosterone (T) ($OR=14.533$, 95% CI : 2.162–97.677, $P=0.006$), SII ($OR=2.030$, 95% CI : 1.079–3.819, $P=0.028$), and LH level on the trigger day ($OR=1.284$, 95% CI : 1.061–1.554, $P=0.010$) were independently associated with PCOS.

Conclusion: Among patients undergoing their first IVF treatment, SII was independently associated with PCOS. This further supported the crucial role of chronic low-grade inflammation in the pathophysiology of PCOS. In the future, its efficacy needs to be verified through large-scale studies. Before it is fully confirmed, it is not recommended to use it as an independent clinical tool.

Keywords: polycystic ovary syndrome, systemic immune-inflammation index, associated factor, reproductive endocrine, antagonist protocol

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder in women of reproductive age, which is characterized by abnormal menstruation, ovarian polycystic changes, and hyperandrogenism.¹ It is often accompanied by insulin resistance, obesity, and increased cardiometabolic risk,² which seriously impair the patient's reproductive health and long-term quality of life.^{3–5} Due to its complex etiology and high heterogeneity of clinical manifestations, the core pathological mechanism is still unclear, and individualized clinical management faces continuous challenges.^{2,6} In recent years, chronic low-grade inflammation has been established as the core pathological basis

connecting multiple metabolic and reproductive abnormalities in PCOS.^{7,8} Therefore, finding biomarkers that can conveniently and objectively evaluate this inflammatory state has become a research hotspot.

Notably, research has shifted from single inflammatory factors, such as C-reactive protein (CRP), to composite indices based on complete blood counts.⁹ Among them, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have attracted attention due to their practicability, but their results in PCOS are inconsistent and susceptible to confounding factors.¹⁰ Systemic immune-inflammation index (SII), which is obtained by integrating platelet, neutrophil and lymphocyte counts, is considered to be a more systematic and stable reflection of the body's immune balance and has shown superior diagnostic value in a variety of chronic inflammatory diseases.^{11,12} However, there are still significant limitations to the evidence for SII in the field of PCOS. A review indicated that most existing studies had used healthy women as the control group, and the sample size was limited, failing to control for the bias caused by inflammation due to infertility.¹³ This significantly limited the ability to interpret the increase in SII levels as a characteristic pathological change of PCOS. The core potential special value of SII in PCOS lied in its integration of platelet count.¹⁴ Platelets were not only passive markers of inflammation, but also key effector cells that were activated and actively amplified inflammation under the condition of PCOS.¹⁵ Patients with PCOS often had elevated platelet counts, which were closely related to insulin resistance and endothelial damage.¹⁶ Activation of platelets could release pro-inflammatory mediators such as interleukin-1 β (IL-1 β), and it worked in synergy with neutrophils to directly act on the ovarian microenvironment, exacerbating the inflammatory infiltration during the follicular development process.¹⁵ In contrast, C-reactive protein only reflected the liver's response to systemic inflammation.¹⁷ Neither NLR nor PLR includes platelets. This further highlighted the unique advantages of SII. Therefore, SII could simultaneously reflect the activation of neutrophils and the platelet-related inflammatory-thrombotic pre-state, thereby providing a more comprehensive reflection of the abnormal "metabolic-inflammatory-coagulation" axis in PCOS. It became an advantageous biomarker for evaluating the local inflammatory load and functional disorders of the ovary. In addition, the heterogeneity of ovarian stimulation protocols, a key confounding factor, has not been adequately accounted for when comparing PCOS women with assisted reproductive technology (ART) and controls.¹⁸ The traditional gonadotropin-releasing hormone (GnRH) agonist protocol will create a "superphysiological" state, significantly alter the endocrine and immune microenvironment, and increase the risk of ovarian hyperstimulation syndrome (OHSS), which may confound the observation of the inherent inflammatory features of PCOS.^{19,20} In contrast, the GnRH antagonist protocol is closer to the physiological state, preserves the natural physiological hormone feedback pathway to the greatest extent, and significantly reduces the risk of OHSS.²¹ It has now become the first choice for ART treatment in patients with PCOS.^{22–24} Therefore, the selection of homogeneous patients receiving GnRH antagonist protocol can effectively exclude the heterogeneous effects caused by different stimulation regimens, and provide an ideal window for accurate assessment of the inherent inflammatory pathological features of PCOS.

To obtain more accurate results, the current study addressed the two limitations of the selection of the control population and the heterogeneity of treatment regimens. This study aimed to compare the demographic and physical indicators, reproductive endocrine indicators, systemic inflammatory indicators, infertility situation, ovulation induction treatment parameters, and trigger day indicators between patients with PCOS and those with unexplained infertility (UI) undergoing the first in vitro fertilization (IVF) treatment with a GnRH antagonist protocol, and to explore the association between SII and PCOS. This study was expected to provide new evidence for further understanding the immune-inflammatory mechanism of PCOS and optimizing its clinical evaluation strategy.

Materials and Methods

Study Design

This study retrospectively analyzed the medical records of 334 women undergoing their first IVF treatment in the Reproductive Medical Center of Lianyungang Maternal and Child Health Hospital, Jiangsu Province, China, from January 2019 to December 2025. All the clinical data of all patients were completed with entry and verification before December 31, 2025. All the included cases had been fully documented, with no cases of missing data. [Figure 1](#) illustrated the detailed process from the initial screening to the final inclusion of 334 patients.

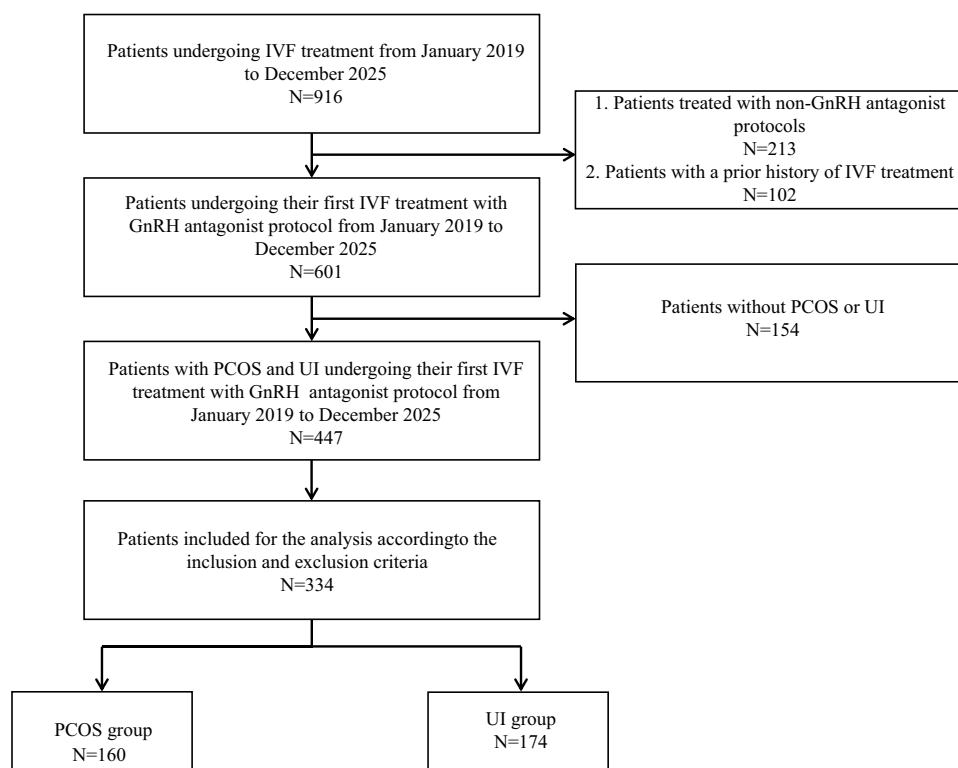


Figure 1 Participant flowchart.

Abbreviations: IVF, in vitro fertilization; GnRH, gonadotropin-releasing hormone; PCOS, polycystic ovary syndrome; UI, unexplained infertility.

Participants

Inclusion and Exclusion Criteria

To control confounding factors and enhance population homogeneity, the following inclusion and exclusion criteria were established in this study. Patients had to meet the following criteria: (1) patients received IVF treatment for the first time; (2) patients were treated with a GnRH antagonist protocol. Patients were excluded if they met any of the following criteria: (1) missing key data; (2) patients with other major infertility factors, including male factor infertility (according to the World Health Organization criteria) or definite tubal infertility; (3) patients with diseases affecting systemic inflammatory state (acute and chronic infections, autoimmune diseases, hematological diseases or pelvic inflammatory diseases) or medication history (use of glucocorticoids, immunosuppressants, non-steroidal anti-inflammatory drugs, oral contraceptives or drugs that may affect metabolism within the past 6 months); (4) patients with other chronic diseases that might interfere with the study, including endocrine diseases (eg, thyroid dysfunction, hyperprolactinemia), hypertension, diabetes, serious organic diseases of the heart, liver and kidney, and malignant tumors; (5) patients with a history of major surgery (including splenectomy history, any surgery in the past 6 months) or specific living habits (such as long-term smoking and drinking habits).

GnRH Antagonist Protocol

All enrolled subjects were treated with the GnRH antagonist protocol. They underwent vaginal ultrasound and sex hormone levels (follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2), testosterone (T)) on day 3 of the menstrual period, and injections of 150 to 250 IU of recombinant human follicle-stimulating hormone (rFSH; follitropin alfa, GonalF, Merck Serono, Rome, Italy) were initiated. Daily injections of 0.125 to 0.25 mg GnRH-ant (Cetrorelix; Merck Group, Darmstadt, Germany) were started when the largest follicle diameter exceeded 12 to 14 mm. Follicle growth was monitored by means of vaginal ultrasound and serum hormone levels (LH, E2, progesterone (P)), and gonadotropin (Gn) doses were adjusted accordingly. Trigger drug injections were given when at least two follicles were ≥ 18 mm in diameter or three follicles were ≥ 17 mm in diameter. Oocyte retrieval was performed 36 hours later.

Grouping

The PCOS group (n=160) was diagnosed based on the Rotterdam criteria,²⁵ which required the presence of at least two of the following three conditions, while excluding other causes of hyperandrogenism (such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors): (1) oligoovulation or anovulation (menstrual cycle >35 days or less than 2 menstrual periods in the past 6 months); (2) clinical or biochemical hyperandrogenism; (3) ultrasound indicates polycystic ovarian changes (single or bilateral ovarian antral follicle count ≥ 20 , and/or ovarian volume ≥ 10 mL). The non-PCOS group (ie, the group of UI, n = 174) was diagnosed according to the guidelines of the European Society of Human Reproduction and Embryology (ESHRE),²⁶ which meant that after a comprehensive assessment of both the husband and the wife (including ovulation monitoring of the female, tubal patency examination, and semen analysis of the male), no clear cause of infertility was found.

Data Collection and Measurement

Demographic and Physical Indicators

Demographic and physical indicators included age and body mass index (BMI). Among them, the BMI calculation formula was weight (kg) divided by the square of height (m).

Reproductive Endocrine Indicators

Reproductive endocrine indicators included anti-Mullerian hormone (AMH), basal FSH, LH, and T. AMH was randomly collected during the menstrual cycle and was tested using the chemiluminescence method (CL-6000i automated chemiluminescence immunoassay analyzer, Mindray, Shenzhen, China). FSH, LH, and T were measured on the 3rd day of the menstrual cycle using an automatic chemiluminescence immunoassay analyzer (Cell-Dyn 3700, Abbott, USA).

Systemic Inflammatory Indicators

Systemic inflammatory indicators included SII, NLR, and PLR. Peripheral venous blood samples were collected before initiating ovarian stimulation. Blood routine analysis was conducted using an automatic blood analyzer (SC-120, Mindray, Shenzhen, China), resulting in the determination of platelet count ($\times 10^9/L$), neutrophil count ($\times 10^9/L$), and lymphocyte count ($\times 10^9/L$). SII was calculated by the formula of platelet count $\times$ neutrophil count / lymphocyte count.²⁷ NLR was calculated by dividing the neutrophil count by the lymphocyte count. PLR was calculated based on platelet count / lymphocyte count.

Infertility Situation

Infertility situation included the type of infertility and the duration of infertility. Type of infertility was classified into primary infertility (defined as a couple having regular sexual intercourse without any form of contraception for at least 12 months, and the woman has never achieved clinical pregnancy) and secondary infertility (defined as a couple having regular sexual intercourse without any form of contraception for at least 12 months, and the woman has had at least one clinical pregnancy in the past, but is currently unable to conceive again).²⁸

Ovulation Induction Treatment Parameters

Ovulation induction treatment parameters included the days of Gn use, the total dose of Gn, and the starting dose of Gn. Among them, the days of Gn use referred to the number of days elapsed from the start date of Gn to the trigger date. The total dose of Gn was the sum of all the doses of Gn used in this cycle. The starting dose of Gn was mainly determined based on the patient's BMI and AMH, after careful consideration.

Trigger Day Indicators

Trigger day indicators included the number of follicles with a diameter of ≥ 14 mm, LH, E2, and P. Among them, the number of follicles with a diameter of ≥ 14 mm was obtained through transvaginal ultrasound examination. All patients underwent a baseline ultrasound examination before ovarian stimulation to rule out pelvic lesions and to measure the antral follicle count (AFC) (the total number of 2 to 5-millimeter-diameter antral follicles) on both ovaries. Ultrasound monitoring during ovulation induction was conducted by trained physicians using an 8 MHz high-resolution vaginal probe.

Data Analysis

Statistical analyses were performed using IBM SPSS version 21.0 (IBM Corporation, Armonk, State of New York, USA) software. Normality of continuous variables was tested using the Kolmogorov–Smirnov test. Normally distributed continuous variables were described with the use of means and standard deviations (SDs), and non-normally distributed continuous variables were described with the use of medians and quartiles. Categorical variables were described as frequencies and percentages. Univariate analysis was performed using *t*-test, non-parametric test, and chi-square test to evaluate the differences of each variable between different groups. The statistically significant variables in univariate analysis were included in the binary logistic regression model to evaluate the independent associated factors of PCOS. To improve clinical interpretability, SII was scaled by dividing by 100 in the binary logistic regression model, and the odds ratio was reported per 100-unit increase. Other continuous variables were presented per their original 1-unit increments. Variables were considered statistically significant at *P* values <0.05.

Ethical Approval and Informed Consent

The study was approved by the Ethics Committee of Lianyungang Maternal and Child Health Hospital (Number: 2024-xm-004). The study implementation adhered to the principles of the Declaration of Helsinki. As this study utilized anonymous medical records for retrospective analysis, patient privacy was protected, and the ethics committee waived written informed consent.

Results

Characteristics of participants

A total of 334 patients were included in this study, including 160 patients with PCOS and 174 patients without PCOS (ie, UI patients). Table 1 presented the demographic and physical indicators, reproductive endocrine indicators, systemic inflammatory indicators, infertility situation, ovulation induction treatment parameters, and trigger day indicators of all patients. The median age of the patients in this study was 31.00 (29.00, 34.00) years, and the average BMI was 23.81 ± 3.68 kg/m². The majority of the patients suffered from primary infertility (64.67%), and the median duration of infertility was 4.00 (2.00, 5.25) years.

Table 1 Characteristics of participants (N=334)

Variable	Total
Demographic and physical indicators	
Age (years)	31.00 (29.00, 34.00)
BMI (kg/m ²) ^a	23.81 ± 3.68
Reproductive endocrine indicators	
AMH (ng/mL)	4.98 (3.09, 8.10)
Basal FSH (IU/L) ^a	5.69 ± 1.61
LH (IU/L)	4.20 (2.80, 6.40)
T (ng/mL)	0.40 (0.30, 0.58)
Systemic inflammatory indicators	
SII	330.71 (233.91, 537.90)
NLR	1.38 (1.08, 2.01)
PLR	122.51 (95.96, 152.60)
Infertility situation	
Type of infertility ^b	
Primary infertility	216 (64.67%)
Secondary infertility	118 (35.33%)
Duration of infertility (years)	4.00 (2.00, 5.25)
Ovulation induction treatment parameters	
Days of Gn use (days)	9.00 (8.00, 11.00)
Total dose of Gn (IU)	1687.50 (1350.00, 2034.38)
Starting dose of Gn (IU)	175.00 (150.00, 187.50)

(Continued)

Table 1 (Continued).

Variable	Total
Trigger day indicators	
Number of follicles with a diameter of ≥ 14 mm on the trigger day (count)	10.00 (7.00, 14.00)
LH level on the trigger day (IU/L)	1.85 (1.13, 3.26)
E2 on the trigger day (pg/mL)	3347.00 (2109.00, 4870.00)
P on the trigger day (ng/mL)	0.60 (0.40, 1.00)

Notes: ^a Continuous variables following a normal distribution; ^b Categorical variables.

Abbreviations: BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; T, testosterone; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; Gn, gonadotropin; E2, estradiol; P, progesterone.

Univariate Analysis of the Associated Factors of PCOS

The univariate analysis showed that there were significant differences between PCOS and non-PCOS in terms of age, BMI, AMH, basal FSH, LH, T, SII, NLR, total dose of Gn, starting dose of Gn, number of follicles with a diameter of ≥ 14 mm on the trigger day, LH level on the trigger day, and E2 on the trigger day ($P < 0.05$) (Table 2).

Table 2 Univariate Analysis of the Associated Factors of PCOS

Variable	PCOS		P
	No	Yes	
Demographic and physical indicators			
Age (years)	32.00 (30.00, 34.00)	30.00 (27.00, 33.00)	0.001
BMI (kg/m^2) ^a	22.50 $\pm$ 3.31	25.23 $\pm$ 3.54	< 0.001
Reproductive endocrine indicators			
AMH (ng/mL)	3.20 (2.22, 4.88)	7.55 (5.44, 11.67)	< 0.001
Basal FSH (IU/L) ^a	6.14 $\pm$ 1.69	5.21 $\pm$ 1.35	< 0.001
LH (IU/L)	3.49 (2.56, 4.80)	5.47 (3.61, 8.50)	< 0.001
T (ng/mL)	0.34 (0.26, 0.47)	0.50 (0.38, 0.67)	< 0.001
Systemic inflammatory indicators			
SII	266.90 (197.61, 328.95)	527.87 (365.38, 746.46)	< 0.001
NLR	1.18 (1.00, 1.40)	1.88 (1.36, 2.78)	< 0.001
PLR	117.21 (99.08, 138.10)	128.23 (92.24, 169.02)	0.078
Infertility situation			
Type of infertility ^b			0.726
Primary infertility	63 (36.21)	55 (34.38)	
Secondary infertility	111 (63.79)	105 (65.63)	
Duration of infertility (years)	4.00 (2.00, 5.00)	4.00 (2.25, 6.00)	0.121
Ovulation induction treatment parameters			
Days of Gn use (days)	10.00 (9.00, 11.00)	9.00 (8.00, 10.00)	0.069
Total dose of Gn (IU)	1800.00 (1500.00, 2175.00)	1575.00 (1275.00, 1909.38)	< 0.001
Starting dose of Gn (IU)	187.50 (150.00, 200.00)	150.00 (150.00, 187.50)	0.001
Trigger day indicators			
Number of follicles with a diameter of ≥ 14 mm on the trigger day (count)	9.00 (6.00, 12.00)	12.00 (8.00, 17.00)	< 0.001
LH level on the trigger day (IU/L)	1.67 (0.97, 2.57)	2.39 (1.27, 4.26)	< 0.001
E2 on the trigger day (pg/mL)	2805.00 (1702.50, 4212.25)	3873.50 (2604.75, 5000.00)	< 0.001
P on the trigger day (ng/mL)	0.60 (0.40, 0.90)	0.60 (0.40, 1.08)	0.376

Notes: ^a Continuous variables following a normal distribution; ^b Categorical variables.

Abbreviations: BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; T, testosterone; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; Gn, gonadotropin; E2, estradiol; P, progesterone.

Table 3 Multivariate Analysis of the Associated Factors of PCOS

Variable	OR	95% CI		P
		Low	High	
Age (years)	0.983	0.869	1.113	0.792
BMI (kg/m ²)	1.130	0.979	1.303	0.095
AMH (ng/mL)	1.437	1.222	1.690	< 0.001
Basal FSH (IU/L)	0.718	0.519	0.993	0.046
LH (IU/L)	1.293	1.100	1.519	0.002
T (ng/mL)	14.533	2.162	97.677	0.006
SII	2.030	1.079	3.819	0.028
NLR	1.571	0.280	8.812	0.607
Total dose of Gn (IU)	1.000	0.999	1.001	0.510
Starting dose of Gn (IU)	0.991	0.974	1.007	0.258
Number of follicles with a diameter of ≥ 14 mm on the trigger day (count)	1.109	0.997	1.233	0.056
LH level on the trigger day (IU/L)	1.284	1.061	1.554	0.010
E2 on the trigger day (pg/mL)	1.000	0.999	1.000	0.333

Abbreviations: BMI, body mass index; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; T, testosterone; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; Gn, gonadotropin; E2, estradiol.

Multivariate Analysis of the Associated Factors of PCOS

The results of the multivariate analysis found that AMH ($OR=1.437$, 95% CI : 1.222–1.690, $P<0.001$), basal FSH ($OR=0.718$, 95% CI : 0.519–0.993, $P=0.046$), LH ($OR=1.293$, 95% CI : 1.100–1.519, $P=0.002$), T ($OR=14.533$, 95% CI : 2.162–97.677, $P=0.006$), SII ($OR=2.030$, 95% CI : 1.079–3.819, $P=0.028$), and LH level on the trigger day ($OR=1.284$, 95% CI : 1.061–1.554, $P=0.010$) were independently associated with PCOS (Table 3).

ROC Curve for SII

The ROC curve analysis demonstrated that the AUC was 0.837 (95% CI : 0.792–0.882, $P<0.001$), indicating that SII could effectively distinguish between the PCOS and non-PCOS groups. The sensitivity and specificity were 0.756 and 0.845, respectively (Figure 2).

Discussion

The complex pathophysiological mechanism of PCOS and the lack of reliable biomarkers continue to pose challenges to its clinical management.²⁹ Chronic low-level inflammation is the core factor driving metabolic and reproductive disorders. The current study evaluated the association between SII and PCOS in a homogeneous group of women who received the first IVF treatment with a GnRH antagonist protocol. The study found that even after controlling for the effects of infertility itself and different stimulation protocols, the SII levels of patients with PCOS were still significantly higher than those in the UI group, and SII was independently associated with PCOS. This discovery provided more direct and specific evidence for the central role of inflammation in PCOS.

The univariate analysis revealed significant differences in SII between patients with PCOS and UI patients. Previous studies have also shown that SII is elevated in PCOS.³⁰ The core contribution of this study lay in its relatively rigorous design. In this study, UI patients were selected as the control group, and the research subjects were limited to those who received the GnRH antagonist protocol that was more in line with physiological hormone feedback. These aimed to minimize the influence of the two major confounding factors, namely “infertility background” and “excessive physiological ovarian stimulation”.^{18,31} The heterogeneity of the previous research results might be partly attributed to these biases that have not been adequately controlled. For instance, the profound pituitary suppression and the hyperphysiological hormonal environment resulting from the traditional GnRH agonist protocol have been demonstrated to independently affect the overall immune and inflammatory status of the body.^{19,20} This might confuse the observation of the inherent inflammatory characteristics of PCOS. This study selected the GnRH antagonist protocol that has become the

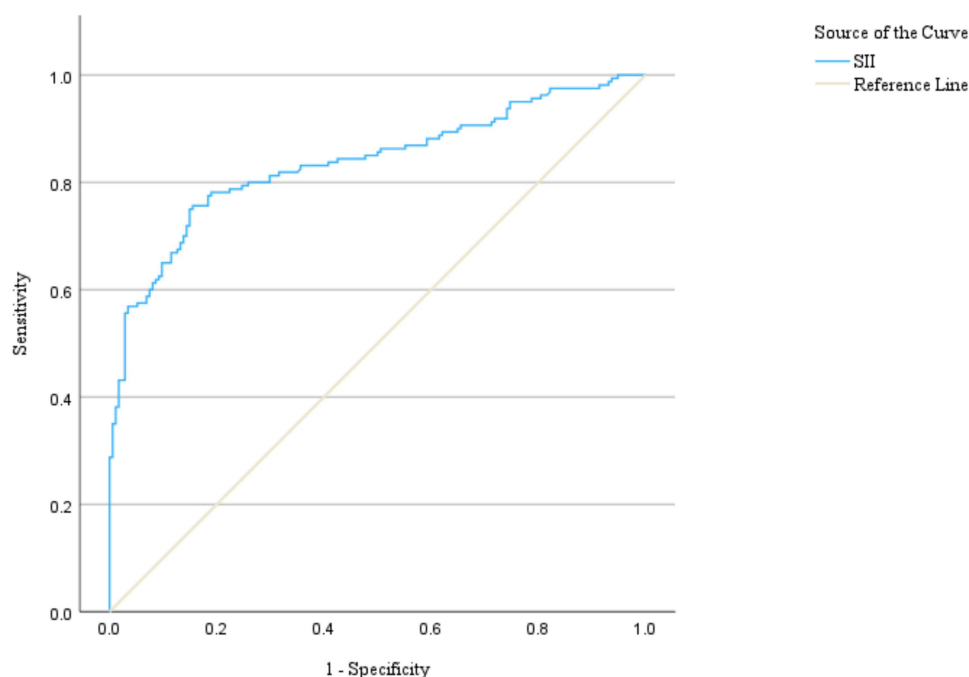


Figure 2 ROC curve for SII.

Abbreviation: SII, systemic immune-inflammation index.

preferred treatment option for ART in patients with PCOS,^{22–24} ensuring that the observed inflammatory differences were more likely to be attributed to the pathological physiological changes of PCOS itself rather than the interference of the treatment intervention.

More importantly, the multivariate analysis revealed that SII was independently associated with PCOS, while NLR and PLR did not show independent association. This highlighted the potential advantages of SII. SII integrates the three key immune-inflammatory pathways of neutrophils, lymphocytes, and platelets, and is considered to be able to more systematically and stably reflect the immune balance state of the body compared to a single ratio.^{11,12} The superiority of SII in this study might have specific pathological and physiological bases. The platelet components in SII demonstrate the synergistic effect of endothelial dysfunction and platelet activation. In the context of chronic low-grade inflammation in patients with PCOS, this synergy occurs through two parallel pathways. On the one hand, pro-inflammatory cytokines (such as interleukin-6 (IL-6)) activate the nuclear factor κ B (NF- κ B) pathway in endothelial cells, upregulate the expression of adhesion molecules, thereby inducing endothelial dysfunction. The clinical manifestations include increased microvascular permeability and impaired vascular dilation function.^{32–34} On the other hand, activated platelets not only release pro-inflammatory mediators, further exacerbating endothelial damage, but also form platelet-leukocyte aggregates through interactions with endothelial cells and white blood cells, thereby continuously driving the local inflammatory microenvironment.^{35,36} In summary, this vicious cycle involving “inflammation-endothelium-platelets” constitutes an important pathological basis for the elevated cardiovascular metabolic risk in patients with PCOS.³⁰ SII may not only reflect the imbalance between innate immunity (neutrophils) and adaptive immunity (lymphocytes),^{37,38} but also indirectly capture the inflammatory-vessel interaction involving platelets in PCOS. This might be a dimension that neither NLR nor PLR has fully captured. The current research findings were highly consistent with the vicious cycle model of chronic low-level inflammation interacting with insulin resistance and hyperandrogenemia in PCOS.^{7,8} It was worth noting that the univariate analysis showed that the BMI of the PCOS group was significantly higher than that of the UI group. However, after eliminating confounding factors through regression analysis, no independent correlation between BMI and PCOS was found. The higher BMI in the PCOS group might not be a direct inflammatory inducer, but rather an external manifestation of underlying metabolic disorders.³⁹ Previous studies have shown that an elevated BMI can indirectly amplify the inherent chronic inflammatory state of PCOS through disorders in the secretion of fat factors.⁴⁰

Furthermore, multivariate analysis also revealed that AMH, basal FSH, LH, T, and LH level on the trigger day were associated with PCOS. This strongly supported the notion that chronic low-grade inflammation was not an isolated phenomenon in PCOS, but rather deeply embedded within the core components of its hypothalamic-pituitary-ovarian axis dysfunction, arrested follicular development, and hyperandrogenemia.^{7,41} In terms of mechanism, when inflammatory factors bind to cell surface receptors, they can activate downstream signaling pathways such as NF- κ B and mitogen-activated protein kinase (MAPK).^{42,43} These pathways, on the one hand, directly regulate the expression of various pro-inflammatory genes, thereby amplifying the inflammatory cascade reactions both locally and systemically. On the other hand, they can also interact with other metabolic signaling pathways through cross-talk.⁴⁴ Inflammatory factors could interfere with the insulin signaling pathway, exacerbating insulin resistance and hyperinsulinemia, and subsequently stimulating the synthesis of androgens in the ovaries and adrenal glands.^{45,46} Conversely, androgens could also promote inflammatory responses through multiple pathways.⁴⁷

From a clinical perspective, this study's findings had significant implications. Firstly, SII was derived from basic blood routine tests, which were readily available and cost-effective. This indicator may be helpful for the auxiliary diagnosis and risk stratification of PCOS patients when they undergo assisted reproductive technology for conception. However, the predictive efficacy and the value of individualized management of this method still need to be confirmed through large-scale prospective studies and external validation. Secondly, the study observed that although the total dose of Gn and the starting dose of Gn were lower in patients with PCOS, they still achieved a greater number of follicles and higher estradiol levels on the trigger day. Specifically, inflammatory factors can activate signaling pathways such as NF- κ B, down-regulate the expression of FSH receptors on granulosa cells, and inhibit the efficiency of downstream signal transduction of FSH receptors.^{48,49} These two aspects of effects ultimately lead to a decrease in the sensitivity of granule cells to FSH. Furthermore, the inflammatory environment may also increase the expression of LH receptors or enhance their sensitivity,⁵⁰ thereby causing the granulosa cells to undergo premature pigmentation. Under the combined influence of these factors, even with a lower dose of exogenous Gn, there is a tendency for excessive follicular recruitment and high secretion of estradiol. This gives rise to a hypothesis that is worthy of further in-depth study and thought in the future: Is the inherent chronic inflammatory state of patients with PCOS caused by altering the local microenvironment of the ovaries or the sensitivity of granulosa cells to Gn, thereby leading to this "high response-low demand" ovulation-promoting pattern? This study provided a possible entry point for subsequent research. Future studies that verify this hypothesis may provide new ideas for developing more individualized and low-risk ovulation induction strategies for PCOS.

Limitations

This study had some limitations. Firstly, this study employed relatively strict exclusion criteria. This design helped to enhance the homogeneity of the research population, thereby enabling a more reliable comparison of key indicators between women with PCOS and those with UI undergoing their first IVF treatment. However, this strict screening process also introduced potential selection bias. Future studies can minimize this bias by adopting broader inclusion criteria. Secondly, as a single-center study, the generalizability of the conclusion needs to be verified in multi-center studies. Thirdly, this study only compared the baseline inflammatory status and ovulation induction treatment parameters of the two groups of patients. It did not further assess whether the inflammatory indicators (such as SII) were associated with key outcomes such as the number of retrieved eggs, embryo quality, clinical pregnancy rate, or live birth rate. Future studies can delve deeper into the correlation between SII and ART outcomes in order to determine whether SII can predict ovarian responsiveness or pregnancy success rates of patients with PCOS, thereby providing more direct evidence for clinical decision-making. Finally, although most of the known confounding factors were strictly controlled through strict exclusion criteria, it was impossible to completely rule out the potential influence of unmeasured lifestyle factors such as dietary patterns, physical activity levels, and psychological stress. Future studies can further elucidate the role of lifestyle factors in the inflammatory manifestations of PCOS by incorporating standardized lifestyle questionnaires, biomarkers, or an intervention-based research design.

Conclusion

In conclusion, through the relatively strict setting and homogenized treatment plans, this study found that SII has an independent association with PCOS in women undergoing their first IVF treatment with a GnRH antagonist protocol. This discovery reinforced the crucial role of chronic low-grade inflammation in the pathophysiology of PCOS. In the future, it is necessary to conduct a systematic evaluation of its predictive performance through large-scale prospective studies and external validation. Furthermore, a more in-depth exploration of the potential value of SII in guiding the individualized clinical management of PCOS patients and predicting the outcome of ART is warranted. However, before thorough verification is conducted, SII should not be regarded as an independent clinical decision-making tool.

Abbreviations

PCOS, polycystic ovary syndrome; SII, systemic immune-inflammation index; IVF, in vitro fertilization; GnRH, gonadotropin-releasing hormone; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; T, testosterone; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ART, assisted reproductive technology; OHSS, ovarian hyperstimulation syndrome; UI, unexplained infertility; E2, estradiol; P, progesterone; Gn, gonadotropin; ESHRE, the European Society of Human Reproduction and Embryology; BMI, body mass index; AFC, antral follicle count; SDs, standard deviations; *OR*, odds ratio; *CI*, confidence interval; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; IL-1 β , interleukin-1 β ; NF- κ B, nuclear factor κ B; MAPK, mitogen-activated protein kinases.

Acknowledgments

We would like to express our gratitude to all those who have contributed to this research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study had no funding support.

Disclosure

The authors declare no competing interests in this work.

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