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Research Article

Unveiling Systemic Immune Inflammation Index Correlations in Women with Polycystic Ovary Syndrome: A Cross-sectional Study

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrinopathy of reproductive-age women that imposes metabolic and cardiovascular risks. Systemic immune inflammation index (SII), an inflammatory biomarker calculated from a complete blood count, was linked to many metabolic and cardiovascular illnesses. ***Objective***: To evaluate the SII correlation with clinical, biochemical, and hormonal parameters characteristic of PCOS cases for screening and diagnostic values. ***Methods***: For fifty PCOS patients who were eligible, we did a cross-sectional study and collected three types of information on each person: demographic information like age, menstrual cycle length, and body mass index (BMI); hormonal information like LH/FSH ratio, testosterone, and fasting insulin; and biochemical information like the homeostasis model assessment of insulin resistance (HOMA-IR), serum cholesterol, serum HDL, and serum LDL. The systemic inflammatory index (SII) was calculated from a complete blood count. ***Results***: We found a strong positive correlation between SII and BMI, LH/FSH ratio, testosterone, fasting serum insulin, HOMA-IR, cholesterol, and LDL. However, the correlation between SII and HDL and menstrual cycle days was negative. Regarding the other parameters (HOMA-IR, testosterone, cholesterol, BMI, and LH/FSH ratio), the best subset regression model figures out how strongly SII is linked to each one. ***Conclusions***: SII was strongly and significantly correlated to PCOS clinical, biochemical, and hormonal parameters, which makes it recommendable for screening. Its feasibility, affordability, and meaningful correlation inspired therapeutic and prognostic applications in practice.

Keywords: Clinical Parameters, Hormonal Parameter, Polycystic ovary syndrome, Screening, Systemic inflammatory index.

الكشف عن ارتباطات مؤشر الالتهاب المناعي الجهازي لدى النساء المصابات بمتلازمة المبيض المتعدد الأكياس: دراسة مقطعية

الخلاصة

الخلفية: متلازمة المبيض المتعدد الأكياس هي اعتلال الغدد الصماء الشائع لدى النساء في سن الإنجاب والذي يفرض مخاطر التمثيل الغذائي والقلب والأوعية الدموية. تم ربط مؤشر الالتهاب المناعي الجهازي (SII)، وهو مؤشر حيوي التهابي محسوب من تعداد الدم الكامل، بالعديد من أمراض التمثيل الغذائي والقلب والأوعية الدموية. **الهدف**: تقييم ارتباط SII بالمعلمات السريرية والكيميائية الحيوية والهرمونية المميزة لحالات متلازمة تكيس المبايض للفحص والقيم التشخيصية. **الطريقة**: بالنسبة لخمسين مريضة بمتلازمة تكيس المبايض، أجرينا دراسة مقطعية وجمعنا ثلاثة أنواع من المعلومات عن كل شخص: المعلومات الديموغرافية مثل العمر وطول الدورة الشهرية ومؤشر كتلة الجسم؛ المعلومات الهرمونية مثل نسبة LH/FSH ، التستوستيرون، والأنسولين الصائم؛ والمعلومات الكيميائية الحيوية مثل تقييم نموذج التوازن لمقاومة الأنسولين، وكوليسترول الدم، و HDL في الدم ، و LDL في الدم. تم حساب مؤشر الالتهاب الجهازي (SII) من تعداد الدم الكامل. **النتائج**: وجدنا علاقة إيجابية قوية بين SII و BMI، ونسبة LH/FSH، والتستوستيرون، والأنسولين في مصل الصيام، و HOMA-IR، والكوليسترول، و LDL. ومع ذلك، كان الارتباط بين SII و HDL وأيام الدورة الشهرية سلبيا. فيما يتعلق بالمعلمات الأخرى (HOMA-IR، والتستوستيرون، والكوليسترول، ومؤشر كتلة الجسم، ونسبة LH/FSH، فإن نموذج انحدار لمجموعة فرعية يحدد مدى قوة ارتباط SII بكل منها. **الاستنتاجات**: ارتبط SII ارتباطا كبيرا بالمعلمات السريرية والكيميائية الحيوية والهرمونية لمتلازمة تكيس المبايض، مما يجعله موصى به للفحص. ألهمت جدواها وقدرتها على تحمل التكاليف ونتائجها ذات المغزى في التطبيقات العلاجية والتنبؤية اثناء الممارسة العملية.

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INTRODUCTION

One of the most prevalent endocrinopathies in modern society is polycystic ovarian syndrome (PCOS). Its exact pathology is not well understood. Genetic, familial, hormonal and environmental factors were blamed as underlying pathologies. Recently, the low grad inflammatory process gained attention as a contributor to PCOS [1–3]. Affected women with hyperandrogenemia demonstrated a disturbed immune response, exhibiting higher levels of inflammatory mediators and activation of various immune cell sub-types such as neutrophils, macrophages, and T-helper lymphocytes [4]. One of those mediators is C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α). Researchers correlated the latter with insulin resistance (IR), obesity, and hyperandrogenemia, which are key factors in PCOS. Higher amounts of TNF-α cause insulin resistance (IR) because it stops insulin signals from getting through, stops glucose from moving, and lowers the expression of proteins that carry glucose. This causes insulin resistance, which is a major cause of PCOS [5,6]. Many scholars have tested inflammatory mediators in the context of PCOS, and many fields of medicine. Systemic immune inflammation index (SII), an inflammatory biomarker that integrates neutrophil, platelet, and lymphocyte levels [7]. It is used to predict malignant disease outcomes and some cardiovascular and metabolic diseases [8–10]. Lately, it has been tested in gynecology and obstetrics in the context of preeclampsia and preterm delivery and has shown promising results [11–12]. Previous research has linked PCOS to low-grade inflammatory biomarkers, yet Iraqi women have not undergone this testing [13,14]. The SII may be able to produce an analysis of the three blood cell types taken from a complete blood count that concurrently mirrors the pathological process underlying PCOS [14]. The current study aimed to investigate the relationship between the SII and the clinical, metabolic, and hormonal parameters that characterize PCOS in Iraqi women, in order to enhance the diagnostic value.

METHODS

Inclusion criteria

The Rotterdam criteria for PCOS diagnosis, which requires the confirmation of two out of three criteria—*first*, oligomenorrhea and chronic anovulation; *second*, a biochemical and/or clinical increase in androgen; and *third*, ultrasonic polycystic ovaries—fit the enrolled cases [15]. To unify the demographic criteria, we included non-married women aged between 20 and 30. We included those with a BMI of less than 30 kg/m^2.

Exclusion criteria

All patients who had previously received insulin-sensitizing therapy or hormonal therapy in the last 6 months were excluded from the study, as were metformin and oral contraceptive drugs. We also excluded cases on steroids and aspirin. We excluded cases with Cushing syndrome, thyroid disease, hyperprolactinemia, and pituitary adenoma. Diabetes, renal, or liver diseases, along with acute or chronic inflammatory illnesses like rheumatoid and inflammatory bowel diseases, are examples of medical conditions. We omitted cases that did not meet the inclusion criteria due to their age range, BMI, medical and drug histories, or incomplete data (Figure 1).

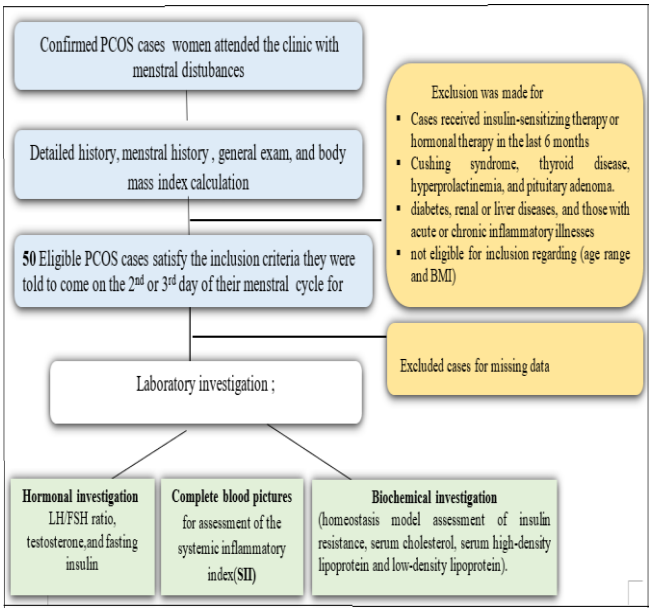

Figure 1: Study flow chart

Outcome measurements

After recording demographic criteria such as age, the estimated duration of the menstrual cycle on the calendar, and BMI, we conducted a detailed history and medical examination. We then instructed the participants to arrive on the 2nd or 3rd day of the MC for their hormonal investigation, which included measuring the LH/FSH ratio, testosterone, and fasting insulin, as well as their biochemical investigation, which included assessing insulin resistance, serum cholesterol, serum high-density lipoprotein, and serum low-density lipoprotein. Following the evaluation of the hormonal and biochemical variables, we sent each participant for a comprehensive blood count to estimate the systemic inflammatory index (SII) using the following equation:

SII (cells/L)= Plt count × neutrophil count/Lymphocyte count × 10^9 [17].

All data (demographic, biochemical and hormonal, and systemic inflammatory index) were preserved in an Excel sheet and stored for further analysis. At the end of the study, 50 patients met the inclusion criteria and were enrolled in the study.

Sample size calculation

The sampling power for cross-sectional studies was calculated as follow [18]:

Sample size = $(Z^{1}\text{-}\alpha/2)^2 \times SD^2/d^2$

Where $Z^{1}\text{-}\alpha/2$ stands for standard normal variate, which is 1.96. SD is the variable standard deviation retrieved from published works. d is the absolute error determined by the operator. The required size is 47.05 participants.

Ethical considerations

The ethical committee of Mustansiriyah Medical College approved the study protocol with the IRB number (48 MOJ) dated 5/3/2023 after obtaining the necessary administrative approval.

Statistical analysis

All data were continuous in type and expressed as mean and standard deviation after checking their normality with the Shapiro-Wilk test. A series of linear regressions with an estimation of the coefficient of correlation (*r*) and its associated value were estimated between SII and all the variables taken in the study. Finally, we conducted the best subset regression to estimate Mallow's coefficient, aiming to gauge the strength of the relationship between SII and the demographic, hormonal, and biochemical variables mentioned above. The interpretation of this coefficient is that the lower value of the Mallow coefficient indicates a stronger association between SII and the variable assessed. All *p*-values less than 0.05 were considered significant.

RESULTS

Table 1 describes the main demographic criteria, hormonal, biochemical, and SII of the 50 PCOS cases recruited in a cross-sectional study.

Table 1: The main characteristics of variables of the participants (n=50)

Variables	Results
Demographic	
Age (year)	25.31±4.23
Mean BMI(kg/m^2)	28.79±1.67
Mean menstrual cycle length (days)	54.38±12.38
Hormonal	
LH/FSH ratio	1.62±0.23
Testosterone	1.59±0.20
Fasting insulin level (µIU/Ml)	31.0±7.15
Biochemical	
HOMA-IR	3.019±0.53
Serum cholesterol (mg/dL)	253.64±39.30
Serum HDL(mg/dL)	39.36±6.51
Serum LDL(mg/dL)	137.52±23.54
Mean SII (× 10^{9}cells/L)	1208.80±214.25

Values were expressed as mean±SD. HOMA-IR: homeostasis model assessment of insulin resistance, HDL, high-density lipoprotein; LDL, low-density lipoprotein.

We conducted a correlation analysis between SII and all the study variables in Table 2. We found a strong positive and significant correlation between SII and several study variables, including BMI, LH/FSH ratio, testosterone, fasting serum insulin, HOMA-IR, cholesterol, and LDL. SII showed an inverse correlation to HDL and menstrual cycle days with an *r*= -0.8 and -0.33 with *p*<0.001 and 0.0187, respectively.

Table 2: Pearson's correlation of various variables in this study with SII (n=50)

Paired variables	*r*	*p*-value
BMI *vs.* SII	0.91	<0.0001
Menstrual cycle length *vs.* SII	-0.33	0.0187
LH/FSH ratio	0.82	<0.0001
Testosterone	0.83	<0.0001
Fasting Serum insulin *vs* SII	0.89	<0.0001
HOMA-IR *vs.* SII	0.95	<0.0001
Cholesterol *vs.* SII	0.87	<0.0001
HDL *vs.* SII	-0.81	<0.0001
LDL *vs.* SII	0.79	<0.0001

BMI; body mass index; HOMA-IR: homeostasis model assessment of insulin resistance, HDL, high-density lipoprotein; LDL, low-density lipoprotein.

In Table 3, The best subset regression model used the Coefficient of Mallow (Cp) to figure out how strongly SII was linked to the study parameters. A stronger link was seen when the Cp value was low. Accordingly, SII had the best association in decreasing order with HOMA-IR, testosterone, cholesterol, BMI, and LH/FSH ratio.

Table 3: Coefficient of Mallow (Cp) between various variables reported in the study (n=50)

Variable *vs.* SII	Cp	Mean sum of Squares
BMI (kg/m^2)	7.3972	1349.43
Menstrual cycle length (day)	1457.52	41708.3
LH/FSH ratio	12.5435	1415.01
Testosterone	2.64	1290.62
Fasting insulin (µIU/ml)	86.25	1558.05
HOMA-IR	1.47	559.28
Cholesterol (mg/dL)	4.79	416.62
HDL (mg/dL)	35.32	667.06
LDL (mg/dL)	81.36	1044.73

DISCUSSION

The analysis showed a strong, meaningful correlation with SII versus PCOS demographic, hormonal, and biochemical parameters. The best association for SII among PCOS cases was for HOMA-IR, followed by testosterone and serum cholesterol. Many researchers examined the role of inflammation among PCOS women and confirmed that affected women do suffer from elevated inflammatory biomarkers, which were associated with PCOS-associated symptoms and complications [3,19]. A cross-sectional study by Cho et al. examined the relationship between SII and IR-related indicators in Korean PCOS women. Their results showed a meaningful relationship between most of the inflammatory biomarkers and IR-related indicators. However, they discussed the impact of anthropometric criteria on those relationships, which reduced the strength of the association [20]. Kuang *et al*. examined inflammatory cytokines among two groups of infertile Chinese women with and without PCOS. The latter group showed an elevated inflammatory cytokine profile, creating a chronic sub-inflammatory status among affected cases. The researchers discussed a negative correlation between cytokines and anti-Mullerian hormone, which disturbs glycolipid metabolism and triggers an IR state,

contributing to PCOS-defining symptoms of irregular cycles and hyperandrogenism [21]. A Mendelian randomized study looked at the link between genetically predicted systemic inflammatory biomarkers and the risk of PCOS in people with European ancestry. Their results highlighted increased PCOS risk among women with high IL-17 and SDF1a levels [22]. Hatziagelak et al. looked at the relationship between a group of low-grade inflammatory mediators and a woman's sexual hormone profile in Greek women with PCOS. They did this while taking age and BMI into account as possible confounders. They postulated a link between inflammatory mediators and PCOS independent of BMI, which could explain the metabolic and cardiovascular risks among cases [23]. The current study showed that the best association of SII was with HOMA-IR, followed by testosterone and serum cholesterol. Özay et al. examined the correlation of inflammatory biomarkers in a comparative study that involved 110 Turkish PCOS cases vs. 135 controls. Their study showed a moderately positive association between neutrophilia versus BMI and HOMA-IR. The best inflammatory marker in their analysis was the C-reactive protein that distinguishes PCOS cases with the highest sensitivity and specificity, $P<0.001$ [24]. Another study proved the efficacy of relative neutrophil count and neutrophil-to-lymphocyte ratio in screening for PCOS among Saudi women. Their findings demonstrated that relative neutrophil count and neutrophil to lymphocyte ratio were independent of participants' hormonal and metabolic criteria, emphasizing the low-grad inflammatory nature of PCOS syndrome [25]. The link between SII mediators and PCOS can be translated into many practical applications. Researchers found that inflammatory mediators (TNF and IL-6, 10, and 18) were higher in overweight-PCOS cases with IR in adolescents with PCOS compared to their normal weight-non-IR peers [26]. The study found a strong and meaningful correlation between HOMA-IR, TG-HDL, and non-HDL in obese children. Their study highlighted the SII role in discriminating children with metabolic syndrome, with a high sensitivity of 83% and a reliable area under the curve [27]. According to the results of the above studies, it is safe to say that SII can serve as a reliable, affordable screening marker for IR and atherogenic risk among younger adults, allowing earlier therapeutic and lifestyle interventions to halt the adult life risk of dyslipidemia, atherogenic complications, and cardiovascular risk. De Medeiros's meta-analysis discussed reducing inflammatory mediators in PCOS cases. They included 27 studies with 383 participants and found that oral contraceptive pills can reduce chronic low-grade inflammation in affected women. However, the study did not address the clinical impact of their result and recommended further work on the topic [28]. Hafizi *et al.'s* meta-analysis included ten studies. Their objective was to investigate the positive impact of physical activity on inflammatory biomarkers in PCOS women. They found that engaging in exercise notably reduced CRP concentration, particularly in women aged 30 years or older and those performing aerobic training [29]. An interesting study by Ezgi *et al*. tested the role of SII as a predictor for threatened abortion cases; cases destined to have miscarriage showed significantly high SII ($p<0.001$). At a cutoff value of 883.9×10^9 cells/L, SII discriminated against the miscarriage group with 60% sensitivity and specificity [30]. As a prognostic marker, the SII role was examined among PCOS cases undergoing IVF to verify the link to the outcome. The highest SII was inversely linked to implantation rates, pregnancy rates (both biochemical and clinical), and live birth rates. Therapeutic strategies can explore and reduce these useful associations of SII in PCOS women to improve IVF outcomes [31]. Researchers suggested that low-grade inflammation, which predisposes affected women to ovarian dysfunction, IR, and other metabolic changes, might be the trigger for PCOS. PCOS cases generally have higher rates of inflammatory mediators such as CRP and IL-6. Although obesity causes a rise in these mediators, they are more elevated in matched BMI - PCOS cases versus matched controls and are also reported among lean PCOS cases. This supports the low grad inflammatory hypothesis, which explains why PCOS arises independently of BMI influence and leads to PCOS-defined hormonal and metabolic misbalance [32–34].

Study limitations

Despite the majority of scholars reporting higher inflammatory biomarkers, some inconsistencies persist, such as in the meta-analysis study of Escobar-Morreale *et al*., potentially due to ethnicity and small sample sizes. The current study did not address ethnicity issues in sampling, which could affect the results [35–37]. The study design is another limitation. Cross-sectional studies assess exposure and results simultaneously, making it difficult to tell which element came first. It is better to undertake longitudinal research to study the causal link and understand PCOS's natural history [38]. PCOS is a heterogeneous syndrome and can have diverse metabolic abnormalities. Currently, standardized values or a defined range for inflammatory indicators in PCOS cases are not available [13].

Strengths of the study

The current study had strict inclusion criteria to standardize and limit confounders' effects in PCOS cases. Multiple associations were defined between SII and metabolic and hormonal parameters, enabling diagnostic and therapeutic interventions. SII served as a screening biomarker among young people and adolescents, resulting in a decrease in the long-term impact of PCOS on maturity. SII evaluated the efficacy of lifestyle changes through exercise and contraceptive pills on the inflammation profile. It demonstrates promising prognostic avenues in IVF and miscarriage cases, paving the way for wider use in practical settings. Compared to other markers of inflammation, such as CRP, SII has a lower cost, providing the added benefit of cost-effectiveness in resource-limited settings, and its combination with the

clinical parameters of the patients can improve its performance [39].

Conclusion

There was a strong correlation between SII and PCOS indicators. The strength of association showed the highest association with HOMA-IR, followed by testosterone, cholesterol, BMI, and LH/FSH ratio in decreasing order. By including SII in PCOS screening, we may be able to learn more about the disease process that causes PCOS. This has increased its potential as a prognostic marker in affected cases to evaluate lifestyle and therapeutic intervention. This test's cost-effectiveness and noninvasive nature added to its meaningful relationship to PCOS parameters, warranting further studies.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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