

A NEW BIOMARKER IN SJOGREN'S SYNDROME? PAN- IMMUNE-INFLAMMATION VALUE AND ITS CLINICAL APPLICABILITY

Sjögren Sendromunda Yeni Bir Biyobelirteç mi? Pan İmmün İnflamasyon Değeri ve Klinik Kullanılabilirliği

Özlem KARAKAŞ¹  Melda AĞIR² 

¹ Division of Rheumatology, Faculty of Medicine, Kırıkkale University, KIRIKKALE, TÜRKİYE

² Clinic of Internal Medicine, Iskenderun State Hospital, HATAY, TÜRKİYE

ABSTRACT

Objective: Primary Sjogren's syndrome (pSS) is a systemic autoimmune disease that primarily affects exocrine glands. The conventional inflammatory markers commonly used to assess disease activity, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), have limited sensitivity. This study aimed to investigate the relationship between the Pan-Immune-Inflammation Value (PIV), disease activity (ESSDAI), and inflammatory markers (CRP, ESR) in patients with pSS.

Material and Methods: This retrospective study included 63 patients diagnosed with pSS according to the 2016 ACR/EULAR criteria and 52 healthy controls. PIV was calculated using neutrophil, monocyte, platelet, and lymphocyte counts at diagnosis. Disease activity was assessed using the EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI), and CRP and ESR levels were recorded. Statistical analysis included the Mann-Whitney U test for group comparisons, Spearman correlation for associations, ROC analysis to evaluate discriminative performance, and univariate logistic regression for effect assessment.

Results: The mean PIV was 329.52±264.32 in the patient group and 291.67±201.54 in the control group (p=0.552). ESR levels were significantly higher in patients compared to controls (p=0.000), while CRP levels did not differ significantly (p=0.093). A weak, non-significant positive correlation was observed between PIV and ESSDAI (rho=0.107, p=0.414), whereas a significant moderate correlation was found between PIV and ESR (rho=0.311, p=0.018). Although the mean PIV was higher in the moderate-high disease activity group, the difference did not reach statistical significance (p=0.071). ROC analysis yielded an AUC of 0.675 for PIV in predicting higher disease activity.

Conclusion: PIV may serve as an indirect indicator of inflammatory activity in pSS. While not sufficient as a standalone marker, it has potential as a complementary biomarker to identify patients with higher systemic disease activity. Further prospective studies with larger sample sizes are warranted.

Keywords: Primary Sjogren's syndrome, PIV, ESSDAI, CRP, ESR, disease activity

ÖZ

Amaç: Primer Sjögren sendromu (pSS), öncelikle ekzokrin bezleri etkileyen sistemik bir otoimmün hastalıktır. Hastalık aktivitesini değerlendirmede yaygın olarak kullanılan C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESR) gibi konvansiyonel inflamatuvar belirteçlerin duyarlılığı sınırlıdır. Bu çalışmada, Pan İmmün İnflamasyon Değeri (PIV) ile hastalık aktivitesi (ESSDAI) ve inflamatuvar belirteçler (CRP, ESR) arasındaki ilişki araştırılmıştır.

Gereç ve Yöntemler: Retrospektif tasarıma sahip bu çalışmaya, 2016 ACR/EULAR kriterlerine göre tanı almış 63 pSS hastası ve 52 sağlıklı kontrol dahil edilmiştir. PIV, tanı anındaki nötrofil, monosit, trombosit ve lenfosit sayılarından hesaplanmıştır. Hastalık aktivitesi, EULAR Sjögren Sendromu Hastalık Aktivite İndeksi (ESSDAI) kullanılarak değerlendirilmiş, CRP ve ESR düzeyleri kaydedilmiştir. İstatistiksel analizlerde grup karşılaştırmaları için Mann-Whitney U testi, ilişkilerin değerlendirilmesinde Spearman korelasyonu, ayırt edici gücün analizinde ROC analizi ve etki değerlendirmesi için univaryant lojistik regresyon analizi kullanılmıştır.

Bulgular: Hasta grubunda ortalama PIV değeri 329,52±264,32, kontrol grubunda ise 291,67±201,54 olarak hesaplanmıştır (p=0,552). ESR düzeyleri hasta grubunda kontrol grubuna göre anlamlı derecede yüksek bulunmuştur (p=0,000), ancak CRP düzeylerinde anlamlı bir fark izlenmemiştir (p=0,093). PIV ile DAI arasında zayıf ve istatistiksel olarak anlamlı olmayan pozitif bir korelasyon (rho=0,107, p=0,414), PIV ile ESR arasında ise anlamlı düzeyde orta şiddette pozitif bir korelasyon saptanmıştır (rho=0,311, p=0,018). Orta-yüksek hastalık aktivitesi grubunda PIV ortalaması daha yüksek bulunmasına rağmen bu fark istatistiksel anlamlılığa ulaşmamıştır (p=0,071). ROC analizinde PIV'nin yüksek hastalık aktivitesini öngörmedeki eğri altı alan (AUC) değeri 0,675 olarak hesaplanmıştır.

Sonuç: PIV, primer Sjögren sendromunda inflamatuvar aktivitenin dolaylı bir göstergesi olabilir. Tek başına yeterli bir belirteç olmasa da, sistemik hastalık aktivitesi yüksek hastaların belirlenmesinde tamamlayıcı bir biyobelirteç olarak potansiyele sahiptir. Daha geniş örneklemli, ileriye dönük çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Primer Sjögren sendromu, PIV, ESSDAI, CRP, ESR, hastalık aktivitesi



Correspondence / Yazışma Adresi:
Division of Rheumatology, Faculty of Medicine, Kırıkkale University, KIRIKKALE, TÜRKİYE
Phone / Tel: +905067883498
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Dr. Özlem KARAKAŞ
E-mail / E-posta: ozlem01us@yahoo.com
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INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands and is commonly observed in the general population.¹ Its prevalence is estimated at approximately 0.5% and incidence at 0.4%.² It has been reported that women are diagnosed eight times more frequently than men.³ In addition to oral and ocular dryness, the disease can affect nearly all organ systems and negatively impact daily functioning due to fatigue, depression, anxiety, and reduced physical performance.⁴ Assessing disease activity and treatment response is critical for the management and follow-up of patients. The European League Against Rheumatism (EULAR) has developed two indices for evaluating disease activity in pSS: 1-The EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI), a self-reported questionnaire for evaluating subjective symptoms; 2-The EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI), which assesses systemic complications through organ-specific clinical criteria.^{5,6} Due to its detailed organ-based structure, ESSDAI is frequently used in clinical studies to evaluate disease activity, particularly when a homogeneous assessment across larger patient cohorts is required.

Inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to monitor disease activity in rheumatic diseases; however, their sensitivity and specificity are limited. In recent years, increasing attention has been paid to the role of hematological markers in assessing disease activity in autoimmune conditions such as SS, systemic lupus erythematosus (SLE), Behçet's disease, and systemic vasculitides.⁷⁻⁹ Blood cells including neutrophils, lymphocytes, platelets, and monocytes are known to play key roles in inflammatory processes.¹⁰

The Pan-Immune-Inflammation Value (PIV) is a novel biomarker calculated by multiplying neutrophil, monocyte, and platelet counts and dividing the result by the lymphocyte count using the formula: $PIV = (\text{neutrophils} \times \text{monocytes} \times \text{platelets}) / \text{lymphocytes}$ (all values $\times 1000/\text{mm}^3$).¹¹ This hematological index measures the overall inflammatory burden and has primarily been validated as a prognostic indicator in various malignancies. With its increasing use in oncology, PIV has also begun to be investigated in rheumatological diseases for its potential association with disease activity.^{12,13}

In this study, we aimed to evaluate whether PIV levels at diagnosis are associated with disease activity (ESSDAI) and laboratory parameters (ESR, CRP) in patients with pSS, and to determine whether PIV can serve as a useful indicator of disease activity and prognosis in this patient group.

MATERIALS AND METHODS

Study Design and Patient Selection

This study was conducted using a retrospective design. A total of 63 patients with a diagnosis of pSS and 52 healthy individuals without any chronic diseases were included. The inclusion criteria were: diagnosis of pSS according to the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria; being under regular follow-up and treatment for at least six months; and willingness to participate in the study.¹⁴

Exclusion criteria included: a diagnosis of rheumatoid arthritis according to the 2016 ACR/EULAR criteria; coexisting autoimmune diseases (e.g., overlap syndromes, scleroderma, inflammatory myopathies); age under 18 years; history of any surgical intervention within the past three months; current corticosteroid therapy; smoking or alcohol use; a history of hematologic or solid malignancies; use of anticholinergic or antidepressant medications; systemic diseases such as hypertension or diabetes mellitus; presence of chronic or active infections; hepatic or renal disorders; and pregnancy or breastfeeding.

The study was approved by the Ethics Committee of Mustafa Kemal University (Approval No: 38, dated June 18, 2025), and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Data Collection

Demographic and clinical data were collected through structured interviews and reviews of medical records. Recorded demographic characteristics included age, sex, comorbidities, and disease duration.

Disease activity was assessed using the EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI). Patients were categorized into two groups based on their ESSDAI scores: remission/low activity (ESSDAI 0–3) and moderate/high activity (ESSDAI ≥ 4).

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels at the time of diagnosis were evaluated for the patient group. For the control group, these values were obtained from routine hospital admission tests.

The Pan-Immune-Inflammation Value (PIV) was calculated using laboratory results from the time of diagnosis in the patient group and from admission values in the control group. PIV was calculated using the formula:

$PIV = \text{neutrophil count } (\times 10^3/\mu\text{L}) \times \text{monocyte count } (\times 10^3/\mu\text{L}) \times \text{platelet count } (\times 10^3/\mu\text{L}) / \text{lymphocyte count } (\times 10^3/\mu\text{L})$.

Treatment regimens were categorized into four groups: patients receiving only conventional disease-modifying antirheumatic drugs (DMARDs), those receiving only biological agents [including CD20 inhibitors, tumor necrosis factor-alpha (TNF α) inhibitors, interleukin

(IL)-6 inhibitors, or Janus kinase (JAK) inhibitors], patients receiving both DMARDs and biologics, and untreated patients.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables were presented as mean \pm standard deviation (SD), while categorical variables were presented as counts and percentages (%).

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to evaluate the normality of CRP, ESR, ESSDAI, and PIV values. Since none of the variables followed a normal distribution ($p < 0.05$), non-parametric tests were used for group comparisons.

The Mann-Whitney U test was applied to assess differences in PIV levels between ESSDAI groups and between patient and control groups. Spearman's correlation test was used to evaluate the relationships between disease duration and ESSDAI, and between disease duration and PIV.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of PIV to discriminate between patients with moderate-high disease activity.

Univariate logistic regression analysis was conducted to examine the effect of CRP, ESR, and PIV on differentiating pSS patients from healthy controls.

RESULTS

Demographic Characteristics

A total of 63 patients diagnosed with pSS and 52 healthy controls were included. The demographic characteristics of the patient and control groups are summarized in table

1. No significant correlations were found between disease duration and ESSDAI ($\rho=0.157$, $p=0.227$), or between disease duration and PIV ($\rho=-0.135$, $p=0.303$).

The mean ESSDAI score was 1.72 ± 3.54 in female patients and 2.5 ± 5 in male patients. No statistically significant difference in ESSDAI scores was found between genders ($p=0.956$). The mean PIV value was 318.00 ± 251.76 in females and 548.46 ± 458.98 in males; this difference was not statistically significant ($p=0.229$).

Commonly reported symptoms included xerophthalmia in 38 patients (60.3%) and xerostomia in 32 patients (50.8%). The most frequent comorbidities were fibromyalgia in 25 patients (39.7%), hypertension in 13 patients (20.6%), and diabetes mellitus in 5 patients (7.9%).

Disease Characteristics

The treatments currently used by the patients are summarized in table 1. The most commonly used DMARD was hydroxychloroquine (84.1%). Patients were divided into two groups based on disease activity: group 1 with remission/low activity ($n=51$, 82.3%), and group 2 with moderate/high activity ($n=11$, 17.7%). ESSDAI scores were significantly lower in the untreated group compared to other treatment groups ($p=0.018$). The mean CRP level in the patient group was 4.11 ± 5.77 mg/L, and the mean ESR was 20.7 ± 12.36 mm/h. In the control group, CRP was 2.82 ± 3.71 mg/L and ESR was 8.59 ± 6.13 mm/h (Table 2). While CRP levels did not significantly differ between the groups ($p=0.093$), ESR levels were significantly higher in the patient group ($p=0.000$) (Figure 1).

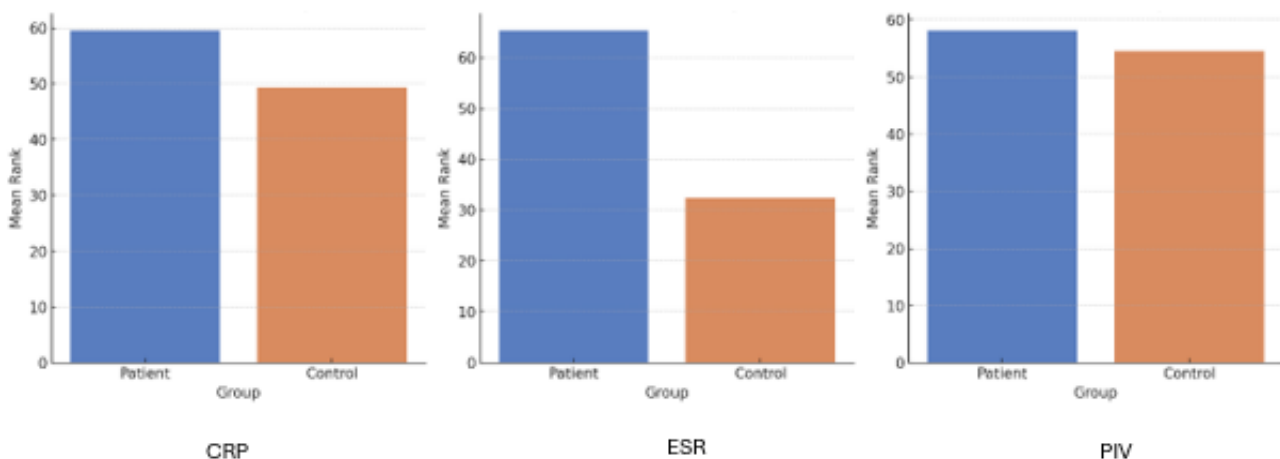


Figure 1: Comparison of mean ranks for CRP, ESR, and PIV between patient and control groups

Comparisons of CRP and ESR levels between activity groups showed no significant differences (CRP: $p=0.554$; ESR: $p=0.086$). The mean PIV value was 329.52 ± 264.32 in patients and 291.67 ± 201.54 in

controls; this difference was not statistically significant ($p=0.552$). A weak positive, but non-significant, correlation was found between PIV and ESSDAI ($\rho=0.107$, $p=0.414$). When stratified by disease

activity, the mean PIV in group 1 (remission/low activity) was 287.02 ± 201.18 , and in group 2 (moderate/high activity) it was 518.86 ± 411.88 . Although the PIV was higher and more variable in group

2, the difference was not statistically significant ($p=0.071$). The area under the ROC curve (AUC) for PIV in predicting disease activity was 0.675, indicating moderate discriminatory power (Figure 2).

Table 1: Demographic and clinical characteristics of participants

	Patients (n=63)	Controls (n=52)
Age, mean \pm SD (years)	52.49 \pm 13.95	35.80 \pm 12.02
Sex, n (%)		
Female	59 (93.7%)	39 (75.0%)
Male	4 (6.3%)	13 (25.0%)
Disease duration, mean \pm SD (years)	5.44 \pm 4.04	-
Common symptoms, n (%):		
Xerophthalmia	38 (60.3%)	
Xerostomia	32 (50.8%)	
Comorbidities, n (%):		
Fibromyalgia	25 (39.7%)	
Hypertension	13 (20.6%)	
Diabetes Mellitus	5 (7.9%)	
Treatment groups, n (%):		
DMARDs only	56 (88.9%)	-
Biologic + DMARD	2 (3.2%)	
No treatment	5 (7.9%)	

Table 2: Comparison of Inflammatory markers between groups

	Patients (Mean \pm SD)	Controls (Mean \pm SD)	p-value
CRP (mg/L)	4.11 \pm 5.77	2.82 \pm 3.71	0.093
ESR (mm/h)	20.7 \pm 12.36	8.59 \pm 6.13	0.000**
PIV	329.52 \pm 264.32	291.67 \pm 201.54	0.552

Table 3: Effects of CRP, ESR, and PIV in Sjogren's Syndrome patients and healthy controls **Univariate logistic regression analysis**

	OR	95% CI	p-Value
CRP	1.020	1.023-1.221	0.720
ESR	0.859	0.814-0.924	0.000
PIV	1.000	0.999-1.001	0.846

Figure 2. ROC Curve for PIV in Predicting Moderate-to-High Disease Activity

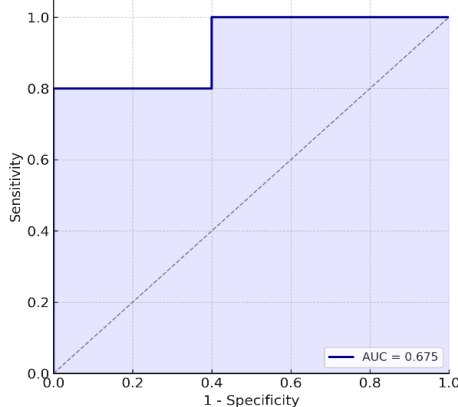


Figure 2: ROC curve for PIV in predicting moderate-to high disease activity

A weak positive but non-significant correlation was found between CRP and PIV ($\rho=0.228$, $p=0.080$). In contrast, a statistically significant moderate positive correlation was found between PIV and ESR ($\rho=0.311$, $p=0.018$).

In univariate logistic regression analysis, CRP ($p=0.720$) and PIV ($p=0.846$) were not significant predictors of pSS compared to healthy controls. However, ESR showed a statistically significant negative association ($p=0.000$), indicating its diagnostic utility (Table 3).

DISCUSSION

In our study, we evaluated the relationship between the Pan-Immune-Inflammation Value (PIV) and disease activity (ESSDAI), CRP, and ESR levels in patients with pSS. Our findings revealed a weak but non-significant positive correlation between PIV and ESSDAI. Similarly, no statistically significant difference was observed in PIV levels between the patient and control groups. However, the mean PIV value was higher in the group with moderate-to-high disease activity, though it did not reach statistical significance ($p=0.071$). Additionally, while there was a weak positive correlation between CRP and PIV, a statistically significant moderate correlation was identified between ESR and PIV ($p=0.018$).

pSS is a systemic autoimmune inflammatory disease characterized by lymphocytic infiltration of the exocrine glands.¹⁵ There is growing interest in the role of hematological and immunological parameters in evaluating and monitoring disease activity in autoimmune diseases. Circulating lymphocytes, monocytes, neutrophils, and platelets are known to play critical roles in many inflammatory processes.^{10,16} Various measurements derived from hematological parameters have been investigated for their ability to reflect inflammation intensity and serve as prognostic markers in inflammatory diseases.¹⁷

PIV is a recently developed biomarker calculated by multiplying neutrophil, platelet, and monocyte counts and dividing the result by the lymphocyte count.¹⁸ While most studies on PIV have been conducted in oncology, limited and conflicting data are available in the field of rheumatology. A study evaluating PIV in rheumatoid arthritis (RA) reported significantly higher PIV levels in active RA patients compared to healthy individuals.¹⁷ However, our study found no significant difference between the patient and control groups. Similarly, a study in sarcoidosis patients showed comparable PIV values between patients and controls.¹⁹ In another study investigating recurrent aphthous stomatitis and Behçet's syndrome, no significant result was observed regarding PIV, whereas another study focusing on vascular Behçet's syndrome reported significantly higher PIV levels in affected patients.^{20,21}

ESR and CRP are widely used inflammatory markers in current rheumatologic practice to detect and monitor disease activity. However, their specificity for rheumatologic diseases is limited.²² ESR may be elevated in physiological or pathological conditions such as acute tissue injury, infections, rheumatic diseases, malignancies, or pregnancy. A previous study comparing CRP and ESR levels with disease activity in pSS patients reported a significant association between these markers and disease activity.²³ In our study, although no significant difference was observed in CRP levels between groups, ESR levels were significantly higher in the patient group, consistent with the literature. Our study is among the limited number of investigations assessing the relationship between PIV and conventional inflammatory markers (ESSDAI, CRP, ESR) in patients with pSS. Although the relationship between PIV and disease activity was not statistically significant, we observed a trend toward higher PIV values in patients with moderate-to-high disease activity. This suggests that PIV may serve as a supplementary biomarker reflecting the inflammatory burden in pSS. The statistically significant correlation between PIV and ESR supports its sensitivity to systemic inflammation.

Although PIV may not be a robust standalone marker, it has potential as a complementary biomarker for identifying patients with higher systemic disease activity in pSS. Additionally, as a non-invasive, easily accessible, and low-cost parameter, PIV may complement traditional inflammatory markers in clinical practice. Future prospective studies with larger sample sizes are warranted to better clarify the association between PIV, disease activity, and prognosis.

This study has several limitations. First, its cross-sectional design prevents the establishment of causal relationships between PIV and disease activity.

Additionally, the relatively small sample size may have limited the statistical power, possibly obscuring some trends from reaching statistical significance. Moreover, the majority of pSS patients in the study were female, and this gender imbalance may restrict the generalizability of the findings. Finally, PIV values were assessed only at a single time point; thus, the dynamic changes of PIV in relation to disease progression could not be evaluated.

Conflict of interest: There is no conflict of interest between the authors.

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Ethical approval: The study was approved by the Ethics Committee of Mustafa Kemal University (Approval No: 38, dated June 18, 2025), and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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