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Pan-immune inflammation value in systemic lupus erythematosus: Is it associated with organ involvement?

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MAIN POINTS

- PIIV were found to be markedly elevated in SLE patients compared with healthy individuals
- Cardiac involvement was associated with elevated PIIV.
- PIIV may reflect both disease activity and organ involvement, indicating its biomarker potential.
- Applying PIIV in clinical practice could assist with risk stratification and guide therapeutic decisions.
- Hydroxychloroquine treatment correlated with lower PIIV, supporting its anti-inflammatory effects in SLE.

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ABSTRACT

Aim: This study aimed to investigate the association between pan-immune inflammation value (PIIV) and both disease activity and organ involvement in patients with systemic lupus erythematosus (SLE).

Materials and Methods: A total of 50 adult SLE patients, meeting the 2019 EULAR/ACR classification criteria, and 35 healthy volunteers were included in the study. PIIV was determined using the formula: [neutrophil × platelet × monocyte] / lymphocyte. Disease activity was evaluated with the SLEDAI-2K index. The relationship between PIIV and clinical findings, organ involvement, laboratory results, and disease activity was assessed.

Results: PIIV levels were markedly higher in SLE patients compared to the control group ($p<0.001$). Patients with cardiac involvement had elevated PIIV values compared to those without heart involvement ($p<0.05$). On the other hand, individuals receiving hydroxychloroquine therapy showed lower PIIV than those not using the drug ($p=0.019$). No clear correlation was observed between PIIV and SLEDAI-2K scores ($p=0.532$).

Conclusion: The findings indicate that PIIV levels are increased in SLE patients compared with healthy controls, suggesting its potential role as a supportive diagnostic marker. Additionally, higher PIIV in patients with cardiovascular involvement and lower values in those treated with hydroxychloroquine imply that PIIV could be considered a useful biomarker for evaluating and tracking cardiovascular risk in SLE.

Keywords: Systemic lupus erythematosus, Pan-immune inflammation value, Disease activity, Cardiac involvement

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder marked by alternating periods of exacerbations and remissions. It can involve multiple organs and systems [1]. Proper evaluation of disease activity is crucial for differentiating flare-ups, preventing irreversible organ damage, and guiding therapeutic decisions. Despite the widespread use of current clinical activity indices, these tools may not fully capture the heterogeneous nature of SLE or accurately indicate specific organ involvement [2, 3].

Alterations in hematologic parameters, including anemia, leukopenia, lymphopenia, and thrombocytopenia, are frequently observed in SLE [4]. Collectively, these cellular alterations provide a strong foundation for the development of novel biomarkers for inflammation. While many investigations have focused on simple binary cell ratios, indices incorporating multiple cell types have only recently begun to be explored [5].

Within this framework, the pan-immune-inflammation value (PIIV) is a straightforward and cost-effective index calcu-

lated from neutrophil, monocyte, platelet, and lymphocyte counts [6, 7]. Originally proposed in oncology settings [8], PIIV has since been studied as a prognostic marker in various chronic inflammatory conditions, including cardiovascular disease [9], obesity, rheumatoid arthritis [5, 10], and Behçet's disease [11]. In recent years, compelling evidence has emerged linking PIIV with cardiovascular risk [7, 9].

There is limited research evaluating the association between PIIV and both disease activity and organ involvement in SLE. Gambichler et al. [12] reported no significant correlation between PIIV and SLE Disease Activity Index (SLEDAI) in adult patients; on the other hand, Alasmari et al. [13] observed a positive association between elevated PIIV and SLEDAI in pediatric lupus cases. In a study by Ulutaş and Çobankara on biopsy-proven lupus nephritis patients, PIIV was examined, but its connection to disease activity was not analyzed [14].

Cardiac involvement in SLE can lead to severe complications, such as pericarditis, valvular disorders, atherosclerotic cardiovascular disease, and heart failure, and represents a major determinant of mortality [15]. Population-based studies have demonstrated strong links between PIIV and cardiovascular outcomes [9, 16]. However, the role of PIIV in predicting cardiac involvement among adult SLE patients has not yet been clearly defined.

Considering the central role of cellular components in SLE immunopathogenesis, PIIV may serve as a useful biomarker for disease monitoring. This study aims to investigate the relationship between PIIV, disease activity, and organ involvement in adult SLE patients.

MATERIALS AND METHODS

This research was conducted as a single-center, cross-sectional, observational study. Fifty adult patients diagnosed with SLE according to the 2019 classification criteria of the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) and 35 healthy controls attending the rheumatology outpatient clinic at Malatya İnönü University between January 2024 and January 2025 were included. The control group comprised healthy volunteers without any signs of rheumatic disease who fulfilled the study's exclusion criteria. This study was approved by the İnönü University Clinical Research Ethics Committee on 11 December 2024 (decision no. 2024/167). All procedures were conducted in accordance with the principles of the Helsinki Declaration.

Individuals younger than 18 or older than 65, as well as those with infections, malignancies, or other rheumatologic conditions, were excluded. Demographic information, clinical features, laboratory parameters, disease activity scores, and treatments of SLE patients were documented. Similarly, demographic and laboratory data were collected for the control group. All participants underwent evaluation of complete blood count, renal function, proteinuria, ANA, ds-DNA, complement levels, CRP, and erythrocyte sedimentation rate. Proteinuria was considered positive when spot urine protein exceeded 300 mg. Disease activity in SLE patients was assessed using SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index-2000), with a score >6 indicating active disease [17,18]. PIIV was calculated using the formula: [neutrophil count × platelet count × monocyte count] / lymphocyte count.

Statistical analysis

Categorical variables were expressed as percentages, summarizing their distribution within the study population. The Shapiro–Wilk test was employed to assess the normality of continuous data. Variables with a non-normal distribution were presented as median (minimum–maximum), whereas normally distributed variables were reported as mean ± standard deviation. For comparisons of categorical variables, the Pearson chi-square test, Yates-corrected chi-square test, or Fisher's exact test was applied as appropriate. Continuous variables were compared between two independent groups using the Mann–Whitney U test and among more than two groups using the Kruskal–Wallis test, where applicable. Associations between continuous variables were evaluated using the Spearman's rank correlation coefficient. A two-tailed p-value <0.05 was considered statistically significant for all analyses. Statistical computations were performed using IBM SPSS Statistics version 26.0 for Windows (IBM Corp., New York, USA).

The minimum required sample size for the study was calculated using the G*Power 3.1 software. Assuming an alpha error of 0.05, a test power (1-β) of 0.80, a moderate effect size of 0.70, and a two-tailed hypothesis for an independent two-sample t-test, at least 34 participants per group (total 68) were required. Therefore, the study included 50 SLE patients and 35 healthy controls, fulfilling the minimum sample size requirement.

RESULTS

Overall, 85 participants were enrolled in the study, including 50 patients (58.8%) and 35 healthy controls (41.2%). The study population consisted predominantly of women (77 individuals; 90.6%), whereas 8 participants (9.4%) were men. Coexisting medical conditions were identified in 39 participants (45.9%), while 46 individuals (54.1%) had no additional health problems. Regarding smoking habits, 13 participants (15.3%) reported active smoking, whereas 72 individuals (84.7%) did not smoke.

The mean age of the study population was 42.73 ± 10.14 years, with a median of 44 years (range, 22–65). The mean body mass index (BMI) was 25.79 ± 4.61, with a median value of 25.59 (range, 15.24–37.97). Among inflammatory markers, the mean erythrocyte sedimentation rate (ESR) was 12.02 ± 16.05 mm/h, with a median of 7 (range, 0.4–116), and the

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Table 1. Demographic, clinical and laboratory characteristics of patient and control groups.

Variables	Patient (n=50)	Control (n=35)	P
Age	42.72±11.27	42.74±8.42	0.992[1]
BMI	25.18±5.24	26.66±3.41	0.120[1]
Sex , M / F, [n (%)]	4 (8.00)/ 46 (92.00)	4 (11.43) /31 (88.57)	0.712[2]
Comorbidity, [n (%)]	35 (70.00)	4 (11.43)	<0.001[3]
Smoking [n (%)]	6 (12.00)	7 (20.00)	0.482[3]
ESR, (mm/hour)	8(2-116)	5(0.4-19)	<0.001[4]
CRP, (mg/dL)	0(0-3.18)	0(0-30)	0.940[4]
WBC, (10^3/uL)	7000(3.24-19440)	6.68(0-6790)	<0.001[4]
Neutrophils,(10^3/uL)	4.7(1.92-15.88)	4.05(2.38-6.97)	0.021[4]
Monocytes (10^3/uL)	0.64(0.32-1.76)	0.5(0.3-1.04)	<0.001[4]
Platelets, (10^3/uL)	285(119-449)	271(176-333)	0.054[4]
Lymphocytes, (10^3/uL)	1.68(0.67-5.1)	2.23(1.54-3.67)	0.001[4]
HB, (g/dL)	12.3(9-17.7)	13.5(10.2-17.1)	<0.001[4]
RDW, [n (%)]	45.1(39-68.9)	41.3(0-47.6)	<0.001[4]
PIIV	498.9(213.2-6512)	235.6(38.5-687)	<0.001[4]

(1): Independent samples t-test , (2): Fisher's exact chi-square test, (3): Chi-square test with Yates correction; (4): Mann Whitney U test [median (max-min)]. BMI: Body Mass Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; WBC: White Blood Cells; Hb: Hemoglobin; RDW: Red Cell Distribution Width; PIIV: Pan-Immune-Inflammation Value.

Table 2. Distribution of PIIV in SLE patients according to demographic, clinical, and laboratory variables.

Variables		PIIV	p
Sex (Male/Female)	M F	778.85(216-1279) 498.9(213.2-6512)	0.497*
BMI	Under 30 Over 30	509.5(213.2-6512) 470.9(285.5-1086)	0.926*
aPL AC	Yes No	612.7(220.8-6512) 441.9(213.2-1279)	0.401*
Comorbidity	Yes No	530.8(213.2-6512) 423.7(216-1232)	0.505*
Smoking	Yes No	418.15(213.2-1279) 509.5(216-6512)	0.676*
SLEDAI>6 and above	Yes No	470.85(220.8-1232) 523.65(213.2-6512)	0.532*
SLEDAI>10 and above	Yes No	506.75(303.9-902.7) 498.9(213.2-6512)	0.979
SLEDAI>20	Yes No	838.4(774.1-902.7) 488.5(213.2-6512)	0.125
Anti Ds DNA	High Low	573.3(216-6512) 461.8(213.2-1086)	0.663*
Low C3	Yes No	423.7(216-902.7) 502.5(213.2-6512)	0.685*
Low C4	Yes No	612.7(313.8-902.7) 488.5(213.2-6512)	0.428*
RF Positivity	Yes No	465.2(410.7-1232) 523.65(216-6512)	0.815*
Presence of proteinuria	Yes No	557.6(285.5-1279) 477.65(213.2-6512)	0.290*

*: Mann Whitney U test; BMI: body mass index; aPL AC: Antifosfolipid anticoagulant; SLEDAI: The Systemic Lupus Erythematosus Disease Activity Index; anti-dsDNA: Anti-double stranded DNA antibody; C3: Complement 3; C4: Complement 4; RF: rheumatoid factor; Pan-immune inflammation value

mean C-reactive protein (CRP) was 0.71 ± 3.29 mg/L, with a median of 0 (range, 0–30).

Regarding haematological parameters, the mean white blood cell (WBC) count was 4,150.49 ± 4,408.36/mm^3, with a median of 4,960 (range, 0–19,440); the mean neutrophil count was 4.64 ± 1.86, with a median of 4.39 (range, 1.92–15.88); and the mean monocyte count was 0.63 ± 0.26, with a median of 0. The mean platelet count was 279 ± 69.59, with a median of 280 (range, 119–449); the mean lymphocyte count was 2.02 ± 0.81, with a median of 1.88 (range, 0.67–5.1); the mean hemoglobin (Hb) was 12.82 ± 1.75 g/dL, with a median of 12.7 (range, 9–17.7); and the mean red cell distribution width (RDW) was 42.82 ± 9.87, with a median of 43.8 (range, 0–68.9).The mean PIIV value was 498.26 ± 713.61, with a median of 318.4 (range, 38.5–6512) (Table 1).

When comparing the patient and control groups, the mean ages were 42.72 ± 11.27 years and 42.74 ± 8.42 years, respectively, with no significant difference observed (p = 0.992). The mean body mass index (BMI) was 25.18 ± 5.24 in the patient group and 26.66 ± 3.41 in the control group, and this difference was not statistically significant (p = 0.120). Regarding gender distribution, the patient group included 4 males (8.0%) and 46 females (92.0%), while the control group comprised 4 males (11.43%) and 31 females (88.57%), with no significant difference detected (p = 0.712). Comorbidities were present in 35 participants (70%) in the patient group and 4 participants (11.43%) in the control group, representing a statistically significant difference (p<0.001). No significant difference was found between the groups with respect to smoking status, as 6 individuals (12%) in the patient group and 7 individuals (20%) in the control group were smokers (p = 0.482) (Table 1).

When comparing laboratory parameters of the patient and control groups, ESR, WBC, neutrophil, monocyte, RDW, and PIIV were considerably increased in the patient group (p<0.001, p<0.001, p = 0.021, p<0.001, p<0.001, p<0.001). In contrast, lymphocyte and hemoglobin levels were reduced

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Table 3. Comparison of PIIV (×10³/μL) according to organ ınvolvement and medication use.

Variables		PIIV Median (Min-Max)	p*
Single and Multiple Organ Involvement	Single organ involvement Multiple organ involvement	481.7(219-1279) 516.5(213.2-6512)	0.806
Lung involvement	Yes No	3643.05(774.1-6512) 488.5(213.2-1279)	0.067
Cardiac involvement	Yes No	786.15(603-6512) 470.85(213.2-1279)	0.042
Gastrointestinal involvement	Yes No	324.35(219-530.8) 509.5(213.2-6512)	0.116
Vasculitis involvement	Yes No	695.4(347-902.7) 488.5(213.2-6512)	0.352
Renal involvement	Yes No	516.5(285.5-6512) 427.9(213.2-1086)	0.186
Neurological involvement	Yes No	318.4(244.7-832.2) 516.5(213.2-6512)	0.166
Hematologic involvement	Yes No	558.6(285.5-1086) 495.3(213.2-6512)	0.967
Joint involvement	Yes No	477.65(213.2-1232) 523.65(219-6512)	0.404
Skin involvement	Yes No	470.1(213.2-1076) 498.9(219-6512)	0.430
Azathioprine use	Yes No	699.5(219-1076) 495.3(213.2-6512)	0.606
Mycophenolate use	Yes No	481.7(218.2-6512) 658.8(213.2-1076)	0.884
Hydroxychloroquine use	Yes No	418.15(213.2-1279) 580.8(216-6512)	0.019
Steroid use	Yes No	481.7(218.2-6512) 699.5(213.2-1086)	0.575
Biologics history	Yes No	774.1(285.5-6512) 427.9(213.2-1232)	0.028*

*:Mann Whitney U test, PIIV: Pan-immune inflammation value.

Table 4. Correlations between PIIV and clinical/laboratory parameters in SLE patients.

Variables		ESR	CRP	WBC	Neutrophils	Monocytes	Platelets	Lymphocytes	Hb	RDW	anti-dsDna	C3	C4	Creatinine
PIIV	r	0.152	0.270	0.265	0.561**	0.447**	0.534**	-0.146	0.021	.320*	0.051	0.116	0.089	-0.077
	p	0.298	0.060	0.063	<0.001	0.001	<0.001	0.311	0.886	0.024	0.726	0.421	0.540	0.596

*p<0.05, **p<0.01; r: Spearman's rho correlation coefficient. PIIV: Pan-Immune-Inflammation Value; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; WBC: White Blood Cells; Hb: Hemoglobin; RDW: Red Cell Distribution Width; anti-dsDNA: Anti-double stranded DNA antibody; C3: Complement 3; C4: Complement 4.

among patients compared with controls (p = 0.001 and p<0.001, in that order). Platelet counts showed a modest elevation in the patient group, yet this variation did not demonstrate a meaningful statistical difference (p = 0.054). CRP concentrations remained comparable across the two groups, with no detectable variation (p = 0.940) (Table 1).

Among SLE patients, the most frequently observed organ involvements were joints (52%, n = 26), kidneys (30%, n = 15), and skin (28%, n = 14). Less common involvements included vascular (8%, n = 4), haematological (14%, n = 7), neurological (14%, n = 7), gastrointestinal (8%, n = 4), pulmonary (4%, n = 2), and cardiac (8%, n = 4) systems. Antiphospholipid antibodies (aPL) were detected in 36.1% of patients (n = 13). Regarding non-biological therapies, 56.0% (n = 28) of patients received combination therapy, while 38.0% (n = 19) were on monotherapy with agents such as steroids, mycophenolate,

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azathioprine, or methotrexate. A small proportion (4%, n = 2) were not receiving any treatment. Specifically, hydroxychloroquine (HCQ) was used by 56% of patients, steroids by 88%, mycophenolate mofetil by 50%, and azathioprine by 22%.

Among SLE patients, the estimated disease duration averaged 9.12 ± 7.41 years, while the median duration was 7.5 years (range 0.1–30). Patient-reported disease activity (Patient-DA) averaged 4.4 ± 2.29, with a median of 5 (range 0–10), while physician-assessed disease activity (Dr-DA) had a mean of 3.74 ± 1.17 and a median of 4 (range 1–6). The average SLEDAI-2K score was 5.32 ± 4.51, with a median of 4 (range 0–20). Serological markers showed a mean anti-dsDNA level of 94.4 ± 145.63, with a median of 30.05 (range 1.1–800). Complement levels were 114.56 ± 30.03 for C3 (median 112.5, range 44–176) and 24.1 ± 13.1 for C4 (median 21.5, range 2–57). The mean creatinine level was 0.87 ± 0.24, with a median of 0.8 (range 0.6–1.9).

The evaluation of PIIV with respect to population profiles and clinical parameters among SLE patients revealed that male participants presented a median PIIV of 778.85 (range: 216–1279), whereas female participants demonstrated a median value of 498.9 (range: 213.2–6512). This variation did not indicate any meaningful statistical difference (p = 0.497). Patients with a BMI below 30 had a median PIIV of 509.5 (range 213.2–6512), compared to 470.9 (range 285.5–1086) in those with a BMI above 30, with no significant difference observed (p = 0.926). Similarly, patients with positive antiphospholipid antibodies (aPL ac) had a median PIIV of 612.7 (range 220.8–6512) versus 441.9 (range 213.2–1279) in those with negative antibodies, showing no significant difference (p = 0.401). When evaluating the presence of comorbidities, patients with additional diseases had a median PIIV of 530.8 (range 213.2–6512), compared to 423.7 (range 216–1232) in those without comorbidities; this difference was also not statistically significant (p = 0.505) (Table 2).

When considering smoking status, the median PIIV among SLE patients who smoked was 418.15 (range 213.2–1279), compared to 509.5 (range 216–6512) in non-smokers, with no statistically significant difference observed (p = 0.676). Among patients with an SLEDAI score of six or higher, the median PIIV was 470.85 (range 220.8–1232), while those with lower scores had a median of 523.65 (range 213.2–6512), showing no significant difference (p = 0.532). Similarly, median PIIV for patients with SLEDAI scores ≥10 and ≥20 were 506.75 (range 303.9–902.7) and 838.4 (range 774.1–902.7), respectively, with neither comparison reaching statistical significance (Table 2)

The analysis revealed no statistically significant associations between PIIV and anti-dsDNA levels, decreased C3, decreased C4, RF positivity, or the presence of proteinuria in patients with SLE (Table 2).

When organ involvement was analyzed, SLE patients with cardiac involvement had a significantly higher median PIIV compared to those without cardiac involvement (p = 0.042). No statistically significant differences were observed for involvement of other organs or systems (p>0.05 for all; Table 3). Median PIIV were 481.7 (range 218.2–6512) for patients using steroids, 481.7 (range 218.2–6512) for those on mycophenolate, and 699.5 (range 219–1076) for patients using azathioprine; none of these differences reached statistical significance. Conversely, patients receiving HCQ had a significantly lower median PIIV of 418.15 (range 213.2–1279) compared to those not using HCQ (p = 0.019). Among patients on combination therapy, the median PIIV was 432.8 (range 218.2–1279), whereas those not taking any non-biological medication had a median of 562.25 (range 216–908.5). Additionally, SLE patients with a history of biological therapy exhibited a significantly higher median PIIV of 774.1 (range 285.5–6512) compared to patients without such therapy, whose median was 427.9 (range 213.2–1232; p = 0.028) (Table 3).

In SLE patients, PIIV demonstrated significant positive correlations with neutrophil (r = 0.561, p<0.001), monocyte (r = 0.447, p = 0.001), platelet counts (r = 0.534, p<0.001) and RDW (r = 0.320, p = 0.024) values. In contrast, no significant correlations were observed between PIIV and hemoglobin (r = 0.021, p = 0.886), C3 (r = 0.116, p = 0.421), C4 (r = 0.089, p = 0.540), or creatinine levels (r = −0.077, p = 0.596). Similarly, PIIV did not show statistically significant associations with CRP (r = 0.270, p = 0.060), WBC (r = 0.265, p = 0.063), or anti-dsDNA levels (r = 0.051, p = 0.726) (Table 4).

DISCUSSION

The present research was conducted to examine the association of PIIV levels with disease activity, organ involvement, and treatment modalities among adult patients with SLE. Our analysis demonstrated that PIIV were significantly elevated in the patient group compared with healthy controls and were particularly higher in those with cardiac involvement. These findings indicate that PIIV may represent a promising biomarker for both diagnostic and prognostic purposes.

SLE is an autoimmune condition that can lead to alterations in hematopoietic stem cells within the bone marrow as well as increased destruction of blood cells in the spleen [19]. Consequently, patients may exhibit variations in circulating blood cell counts, either directly related to the disease itself or associated with disease activation [20]. The alterations in these cells' counts are clinically important, as they contribute both to the diagnosis of SLE and to the evaluation of disease activity. Moreover, the magnitude of change in each cell type varies depending on the degree of disease activation and the specific organ or system involved.

Beyond assessing individual cell counts, previous studies have suggested that simple and cost-effective hematological indices—calculated by comparing these parameters—hold potential as biomarkers [21, 22]. Within this framework, the

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PIIV index, which reflects proportional shifts across multiple immune cell lines, has emerged as a candidate biomarker for systemic inflammatory disorders such as SLE, where nearly all circulating immune cells are affected.

The PIIV index was originally proposed as a tool to estimate clinical outcomes and prognosis in oncological disorders. Indeed, several studies have demonstrated its prognostic value in malignancies, including advanced colorectal cancer, hepatocellular carcinoma, and breast cancer [6, 23, 24]. More recently, evidence has emerged supporting its potential role in rheumatic inflammatory diseases, not only for diagnostic purposes but also in evaluating disease activity [5, 10, 11, 13, 14].

In the present study, PIIV levels were found to be higher in adult SLE patients compared with the control group. Nevertheless, no statistically significant correlation was observed between PIIV and SLEDAI scores. Similarly, PIIV did not differ significantly between patients with active disease (SLEDAI > 6) and those without.

To date, three studies have explored the potential utility of PIIV in SLE. Among these, one was performed in paediatric patients and another in individuals with lupus nephritis (LN) [13, 14]. Furthermore, Gambichler et al. evaluated 148 SLE patients, 48 individuals with hidradenitis suppurativa, and 35 control subjects, and found that PIIV were markedly higher in the SLE group relative to the control group [12]. This outcome is consistent with our results and strengthens the concept that PIIV may function as a supportive biomarker in identifying SLE. However, in that study, PIIV showed no significant association with SLEDAI-2K, and only ANA titres >1:640 were identified as predictive for disease flares. Consistently, in our analysis, PIIV was not significantly related to conventional activity parameters, including SLEDAI scores, dsDNA levels, complement (C3 and C4) concentrations, or proteinuria. Taken together, these data suggest that although PIIV levels may rise in SLE, they may have limited capacity to directly mirror disease activity.

Similarly, in a study by Alasmari et al. involving 125 pediatric patients with SLE, those with baseline PIIV exceeding 250 were reported to have higher SLEDAI scores [13]. An important limitation of that study, however, was its restriction to a pediatric population and the absence of a healthy control group.

In another case–control study, Ulutaş et al. evaluated 45 patients with biopsy-proven lupus nephritis (LN) [14]. PIIV was calculated before the initiation of any immunomodulatory or immunosuppressive treatment, and higher baseline PIIV was found to be associated with reduced glomerular filtration rate (GFR) in LN patients. Nevertheless, this study focused exclusively on renal involvement and did not account for other organ manifestations of SLE. In addition, the relationship between PIIV and disease activity indices was not explored, as the analysis was limited to its association with GFR [14].

In our study, PIIV were significantly higher in SLE patients with cardiac involvement compared with those without, whereas no association was observed between PIIV and other organ involvements. By contrast, Alasmari et al. reported elevated PIIV in pediatric SLE patients with renal, hematological, musculoskeletal, and mucocutaneous manifestations, but no significant difference between those with and without cardiac involvement [13]. Taken together, these findings highlight a discrepancy between the two studies regarding the relationship between PIIV and organ involvement. We propose that this inconsistency may stem from differences in disease course between pediatric and adult SLE, as well as developmental variations in bone marrow cell production and peripheral cell destruction processes during childhood compared with adulthood [25, 26].

Conversely, accumulating evidence has demonstrated strong associations between PIIV and adverse cardiovascular outcomes, including cardiovascular mortality, heart failure, and coronary artery disease [9, 27]. In SLE, programmed cell death pathways—particularly NETosis and pyroptosis have been shown to contribute to cardiac involvement by amplifying systemic inflammation and promoting myocardial injury [16].

Plasmacytoid dendritic cell (pDC) activation in SLE patients further exacerbates this process through excessive secretion of type I interferons (IFNs) [28, 29]. These cytokines not only impair the balance between endothelial damage and vascular repair but also stimulate the production of multiple pro-inflammatory interleukins and cytokines, enhance plaque instability, and facilitate prothrombotic events via platelet activation. Sustained IFN signaling has therefore been recognized as a central mechanism driving accelerated atherosclerosis in SLE [30]. In light of these findings, the significantly higher PIIV levels observed in our patients with cardiac involvement suggest that PIIV may serve as a potential biomarker reflecting cardiovascular risk in SLE.

HCQ represents a cornerstone therapy for autoimmune conditions such as systemic lupus erythematosus, with established cardioprotective effects. HCQ modulates both the number and function of peripheral blood cells by influencing multiple signaling pathways and suppressing antigen presentation. Specifically, HCQ inhibits type I interferon (IFN) signaling from plasmacytoid dendritic cells (pDCs) and prevents endosomal activation of Toll-like receptors 7 and 9, thereby reducing cytokine production [31]. This inhibition attenuates the IFN signaling pathway, a critical component in SLE pathogenesis, and decreases expression of IFN-regulatory genes, ultimately limiting both innate and adaptive immune activation. At the lymphocyte level, HCQ interferes with Ca^{2+} release from the endoplasmic reticulum, resulting in multi-level suppression of T and B cell activation and dampening the overall immune response [32, 33].

In our cohort, analysis of non-biological treatment subgroups revealed that only patients receiving HCQ exhibited signif-

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icantly lower PIIV. This observation can be explained by HCQ's dual effect of increasing lymphocyte counts (denominator of the PIIV formula) while simultaneously suppressing neutrophils, monocytes, and platelets (numerator). The concurrent presence of elevated PIIV in patients with cardiovascular involvement and reduced PIIV in those on HCQ highlights the potential utility of the PIIV index as a biomarker for assessing and monitoring cardiovascular risk in SLE.

Key aspects of our study include the inclusion of both SLE patients and healthy controls, the calculation of PIIV using detailed hematological data, and the comprehensive comparison of clinical and laboratory parameters. Special attention was given to cardiac involvement, which has been assessed in only a limited number of previous studies.

Limitations

However, several limitations should be noted. The study was single-center, and the sample sizes for some subgroups, particularly those with cardiac involvement (including tamponade, pericarditis, and myocardial infarction), were very small, limiting the ability to perform separate analyses for each cardiac subtype; therefore, prospective studies evaluating each cardiac subtype separately are warranted. Future prospective studies with larger SLE populations, detailed assessment of cardiovascular risk factors, and regular PIIV evaluations using cardiovascular imaging are needed to better understand the clinical relevance of PIIV.

CONCLUSION

Our findings indicate that elevated PIIV in SLE patients compared to healthy controls may support its role as a diagnostic biomarker. Furthermore, the observation that PIIV is higher in patients with cardiovascular involvement and lower in those receiving HCQ suggests that PIIV could be a useful marker for predicting and monitoring cardiovascular risk, a significant contributor to morbidity and mortality in SLE.

Ethics Committee Approval: The study was approved by the İnönü University Clinical Research Ethics Committee on 11 December 2024 (decision no. 2024/167).

Informed Consent: Informed consent was obtained from all participants.

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Conflict of Interest: The authors have no conflict of interest to declare.

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