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Pan-immune-inflammation value and systemic immune-inflammation index: Are they useful markers in sarcoidosis?

Adem Ertürk [1], Aydın Balcı [2]

[1] Afyonkarahisar Health Sciences University, Department of Rheumatology, Afyonkarahisar, Turkey
[2] Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Chest Diseases, Afyonkarahisar, Turkey

ORCID ID of the author(s)

AE: 0000-0001-8882-0692
AB: 0000-0002-6723-2418

Corresponding Author
Adem Ertürk
Afyonkarahisar Health Sciences University, Department of Rheumatology, Afyonkarahisar, Turkey
E-mail: drademerturk@hotmail.com

Ethics Committee Approval
The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (date: March 3, 2023, number: 2023/130).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Sarcoidosis is a multisystem inflammatory disease characterized by the infiltration of various organs. Due to the lack of a widely-accepted biomarker, researchers have explored alternative and previously unexplored parameters in sarcoidosis. This study aimed to investigate the utility of various markers, including the systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV), in patients with sarcoidosis.

Methods: A case-control study was conducted between January 2019 and February 2023. The study included 75 patients diagnosed with sarcoidosis, and 93 healthy individuals matched for age, sex, and body mass index. Sarcoidosis-related features, such as lung stage and extrapulmonary involvement, were recorded. The researchers investigated SII, PIV, procalcitonin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), other biochemical results, and complete blood counts (including neutrophil, lymphocyte, monocyte, platelet counts, hemoglobin, mean platelet volume [MPV], and red cell distribution width [RDW]).

Results: The age and sex distribution were similar in both the case and control groups (P=0.258 and P=0.196, respectively). The patient group had a significantly lower absolute lymphocyte count than the control group (P=0.035). Patients' RDW (P=0.007), platelet-to-lymphocyte ratio (P=0.028), and ESR (P<0.001) values were significantly higher compared to controls. No significant difference was observed between the two groups regarding other variables, including PIV and SII. There was a significant weak positive correlation between PIV and lung stage, as well as between MPV and the presence of erythema nodosum.

Conclusion: PIV and SII values in patients with sarcoidosis were similar to controls. The positive correlations between PIV and lung stage and between MPV and erythema nodosum suggest potential relationships with sarcoidosis-related features and demonstrate the value of these readily available and inexpensive markers in patient management. Comprehensive studies are needed to clarify whether SII and/or PIV can be used to assess the characteristics of patients with sarcoidosis.

Keywords: sarcoidosis, pan-immune-inflammation value, systemic immune-inflammation index, pulmonary sarcoidosis

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Introduction

Sarcoidosis is a multisystem disease characterized by infiltrating various organs with non-necrotizing granulomas [1]. It is estimated to have an annual incidence of approximately 2.3 to 11 cases per 100,000 people [2]. Patients diagnosed with sarcoidosis generally have a shorter life expectancy than the general population [3,4], and certain populations face a particularly high mortality risk [5].

Sarcoidosis exhibits heterogeneous manifestations [1,6]. It can be asymptomatic or present with non-specific symptoms such as fatigue [7], mild-to-moderate respiratory symptoms (cough, dyspnea, and chest pain), lymphadenopathy, fever, weight loss, and night sweats [1,6]. Asymptomatic patients are sometimes incidentally detected through lung X-rays ordered for other reasons. Patients presenting with non-specific symptoms like fatigue and lymphadenopathy require a differential diagnosis to exclude lymphoma, leishmaniasis, toxoplasmosis, and tuberculosis [1,8]. The clinical presentation's heterogeneity and the numerous potential differential diagnoses make the disease challenging to diagnose. Additionally, predicting the disease's course and treatment response appears to be difficult [9].

The etiology and pathogenesis of sarcoidosis remain unclear, but there is increasing research into the mechanisms involved in granuloma formation, including genetic predisposition, environmental factors, and infectious triggers [1,10,11]. While it has been suggested that immune system overactivation may play a significant role in forming granulomas responsible for the disease's clinical manifestations, our understanding of immune-related mechanisms remains limited [10]. Numerous clinical, physiological, radiographic, histological, and serological parameters have been investigated to identify potential disease-specific biomarkers that can aid in the diagnosis, classification, and prognosis of sarcoidosis. Many parameters have shown significant alterations in patients with sarcoidosis [4,12,13]. However, a common characteristic of many of these parameters is their low sensitivity and specificity.

The pan-immune-inflammation value (PIV) has recently emerged as a novel prognostic predictor for certain diseases. PIV is calculated using an equation that incorporates neutrophil, platelet, monocyte, and lymphocyte counts [14]. Studies have demonstrated that PIV serves as an important indicator of mortality and/or prognosis in various conditions, including different cancers [15], myocardial infarction [16], antineutrophil cytoplasmic antibody-associated vasculitides [14], membranous nephropathy [17], chemotherapy response [18], and steroid response in idiopathic IgA nephropathy [19]. Additionally, the systemic immune-inflammation index (SII), which is similar to PIV and derived from neutrophil, platelet, and lymphocyte counts, has shown predictive capabilities for prognosis and/or disease severity in diverse conditions such as various cancers [20], membranous nephropathy [17], subarachnoid hemorrhage [21], carotid stenosis [22], and acute pulmonary embolism [23]. However, to our knowledge, the predictive roles of these two prognostic markers in the diagnosis, clinical features, and severity of sarcoidosis have not been investigated previously.

The absence of a widely-accepted biomarker has prompted research into alternative and previously unexplored parameters in sarcoidosis. In this study, our primary objective was to examine the predictive capabilities of SII and PIV in diagnosing sarcoidosis. Additionally, we aimed to explore potential correlations between various biomarkers, including PIV and SII, and the clinical features and severity of sarcoidosis as secondary objectives.

Materials and methods

Ethical statement

The ethical protocol for this study was approved by the local ethics committee with a decision date of 03.03.2023 and decision number 2023/130. All procedures were conducted in compliance with the ethical standards set forth by the institutional research committee, as well as the Helsinki Declaration and its subsequent amendments.

Study design and setting

This case-control study was conducted at the Department of Rheumatology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, spanning from January 2019 to February 2023.

Study population

Based on descriptive statistics from Kemal et al.'s study [24] (effect size=0.577), a sample size of 65 participants per group (total of 130) was determined to achieve 90% power at a two-sided significance level of 0.05. The sample size calculation was performed using a two-sample t-test power analysis (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

The study included a total of 75 patients diagnosed with sarcoidosis (patient group) and 93 healthy individuals (control group). The control group was selected randomly from individuals who visited the internal medicine or rheumatology outpatient clinic for various reasons. These individuals had no known diseases and were not diagnosed with any conditions after undergoing necessary examinations. Age, sex, and body mass index were matched between the control group and the patient group.

Common exclusion criteria for both groups were under 18 years of age, having an active infection at the time of blood sample collection, having a known immunological or rheumatological disease, and being diagnosed with any confounding comorbidity such as diabetes, hypertension, chronic kidney failure, chronic liver failure, cardiovascular disease, metabolic disease, or malignancy.

Data collection

The age and sex information of the participants was documented. Measurements of height (in cm) and weight (in kg) were taken, and body mass index was calculated using the formula weight/height^2 (in kg/m^2). Smoking status was queried among the patients; however, due to missing data in the smoking information collected from the control group, this variable was not included in the study. Blood test results for all participants and sarcoidosis-related characteristics of the patient group were obtained retrospectively from the computerized database records of our hospital.

Sarcoidosis diagnosis, management, and related definitions

Confirming sarcoidosis diagnosis involved obtaining tissue samples from patients suspected of having sarcoidosis, supported by clinical and radiological evidence. This was achieved through procedures such as endobronchial ultrasound, mediastinoscopy, and biopsies of the skin and axillary lymph nodes. These samples were analyzed to identify the presence of non-caseating granulomas while excluding other potential causes of these granulomas, as previously documented [1,6]. All pathological analyses were conducted in the pathology laboratory of our hospital. In cases where patients did not consent to biopsy and/or presented with Löfgren's syndrome, the diagnosis of sarcoidosis was made based on clinical, radiological, and laboratory findings in accordance with established criteria [25].

Sarcoidosis staging was determined by analyzing radiological images of the lungs using the Siltzbach classification system. This system categorizes sarcoidosis into five stages as follows: Stage 0, which indicates a normal appearance on chest X-ray; Stage 1, characterized by the presence of bilateral hilar lymphadenopathy; Stage 2, where bilateral hilar lymphadenopathy is accompanied by parenchymal involvement; Stage 3, indicating parenchymal involvement without bilateral hilar lymphadenopathy; and Stage 4, denoting the presence of pulmonary fibrosis [26].

Extrapulmonary involvement was diagnosed based on established general and organ-specific guidelines and studies, as mentioned previously [1,27–30].

Sarcoidosis treatment and follow-up management were conducted following the guidance provided by previous studies that describe treatment approaches [6,31].

Blood analysis

All laboratory analyses were conducted at the Biochemistry Laboratory of Afyonkarahisar Health Sciences University Hospital, utilizing calibrated standard measuring devices and adhering to the manufacturer's recommendations and international standards. The study incorporated routine laboratory results of patients following histopathological diagnosis and those of the control group during their outpatient clinic admission. No additional blood samples were collected specifically for the study, and no laboratory analyses exclusive to the study were performed. The measured laboratory parameters encompassed procalcitonin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), calcium levels, and a complete blood count, which involved assessing absolute neutrophil, lymphocyte, monocyte, and platelet counts, as well as hemoglobin level, mean platelet volume (MPV), and red cell distribution width (RDW).

Inflammation-related indexes

The systemic immune-inflammation index was calculated using the following formula: SII=Absolute neutrophil count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [32].

Pan-immune-inflammation value was calculated using the following formula: PIV=Absolute neutrophil count ($\times 10^3$) × Absolute monocyte count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [14].

Also, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) were calculated.

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was employed for all analyses conducted in this study. The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as mean (standard deviation) or median (1st quartile - 3rd quartile), depending on their distribution, while categorical variables are presented as frequency (percentage). For normally distributed variables, independent samples t-tests were performed, whereas non-normally distributed variables were analyzed using the Mann-Whitney U test. The chi-square test was used to analyze categorical variables. The discrimination performance of variables was evaluated through Receiver Operating Characteristic (ROC) curve analysis, and the optimal cut-off points were determined using the Youden index. Spearman correlation coefficients were calculated to assess the relationships between variables. A *P*-value of <0.05 was considered statistically significant.

Results

The median age of the patient group was 55 years (42–62 years), and that of the control group was 56 years (46–60 years) (P=0.258). Among the patient group, 72.00% (n=54) were female, while 61.29% (n=57) of the control group were female (P=0.196). Table 1 summarizes the differences in variables between the patient and control groups, as well as the distribution of characteristics in the patient group. Accordingly, the absolute lymphocyte count of the patient group was significantly lower than that of the control group (P=0.035). The RDW (P=0.007), PLR (P=0.028), and ESR (P<0.001) of the patient group were significantly higher than those of the control group. No significant difference was observed between the two groups in terms of other variables, including PIV (P=0.204) and SII (P=0.201).

Using a cut-off value of ≥14, the sensitivity of RDW in distinguishing patients with sarcoidosis from healthy individuals was 51.35%, and the specificity was 70.97% [P=0.007, AUC (95.0% CI)=0.621 (0.533–0.708)]. It was observed that PLR exhibited a sensitivity of 36.00% and a specificity of 94.62% with a cut-off value of ≥171 [P=0.028, AUC (95.0% CI)=0.599 (0.509–0.688)] (Table 2, Figure 1).

The present study in patients with sarcoidosis found a significant correlation between PIV and stage (r=0.294, P=0.010), as well as between PIV and erythema nodosum (r=-0.280, P=0.015), and uveitis (r=-0.257, P=0.026). SII also showed a significant correlation with erythema nodosum (r=-0.293, P=0.011). Additionally, PLR was found to be significantly correlated with dactylitis (r=-0.251, P=0.030), MLR with erythema nodosum (r=-0.280, P=0.015), NLR with erythema nodosum (r=-0.319, P=0.005), dactylitis (r=-0.255, P=0.028), and myositis (r=-0.248, P=0.032). MPV showed a positive correlation with erythema nodosum (r=0.308, P=0.008), and procalcitonin showed a correlation with uveitis (r=-0.277, P=0.017). Furthermore, there was a significant moderate positive correlation between PIV and CRP (r=0.477, P<0.001),

PIV and ESR (r=0.439, *P*<0.001), ESR and RDW (r=0.574, *P*<0.001), SII and ESR (r=0.403, *P*<0.001), and SII and CRP (r=0.483, *P*<0.001) (Table 3).

Table 1: Demographic, clinical and laboratory features of patients with sarcoidosis and healthy controls

	Patients (n=75)	Controls (n=93)	*P*-value
Age (years)	55 (42 - 62)	56 (46 - 60)	0.258
Sex			
Male	21 (28.00%)	36 (38.71%)	0.196
Female	54 (72.00%)	57 (61.29%)	
Body mass index (kg/m^2)	30.24 (25.86 - 33.30)	30.06 (24.75 - 32.03)	0.101
Smoking status			
Smoker	8 (10.67%)	-	-
Non-smoker	62 (82.67%)	-	
Ex-smoker	5 (6.67%)	-	
Hemoglobin (g/dL)	13.26 (1.70)	13.54 (1.76)	0.300
Neutrophil (x10^3)	4.76 (3.76 - 5.89)	4.88 (3.67 - 5.98)	0.595
Lymphocyte (x10^3)	1.82 (1.34 - 2.54)	2.11 (1.72 - 2.59)	**0.035**
Monocyte (x10^3)	0.59 (0.44 - 0.70)	0.57 (0.43 - 0.69)	0.991
Platelet (x10^3)	268 (226 - 334)	252 (219 - 293)	0.177
Procalcitonin (ng/mL)	0.27 (0.24 - 0.33)	0.25 (0.23 - 0.31)	0.139
Mean platelet volume (fl)	10.3 (9.7 - 10.8)	10.1 (9.4 - 10.9)	0.897
Red cells distribution width (%)	14.0 (13.1 - 15.1)	13.2 (12.8 - 14.1)	**0.007**
Neutrophil-to-lymphocyte ratio	2.43 (1.74 - 3.41)	2.53 (1.69 - 3.37)	0.509
Monocyte-to-lymphocyte ratio	0.30 (0.22 - 0.40)	0.28 (0.19 - 0.39)	0.245
Platelet-to-lymphocyte ratio	142.79 (104.64 - 202.21)	131.61 (106.12 - 155.92)	**0.028**
Systemic immune-inflammation index (x10^3)	626.24 (443.60 - 1076.04)	582.65 (430.00 - 826.86)	0.201
Pan-immune-inflammation value (x10^6)	350.43 (229.07 - 677.91)	339.70 (197.33 - 531.25)	0.204
Erythrocyte sedimentation rate (mm/h)	24 (11 - 38)	12.5 (7 - 20)	**<0.001**
C-reactive protein (mg/L)	0.7 (0.3 - 3.55)	0.7 (0.3 - 2.4)	0.594
Calcium (mg/dL)	9.40 (9.06 - 9.67)	9.32 (8.97 - 9.63)	0.342
Stage			
Stage 1	15 (20.00%)	-	-
Stage 2	32 (42.67%)	-	
Stage 3	21 (28.00%)	-	
Stage 4	7 (9.33%)	-	
Erythema nodosum	16 (21.33%)	-	-
Uveitis	16 (21.33%)	-	-
Neurosarcoidosis	5 (6.67%)	-	-
Ankle arthritis	25 (33.33%)	-	-
Arthritis in another site from ankle	16 (21.33%)	-	-
Arthralgia	50 (66.67%)	-	-
Dactylitis	3 (4.00%)	-	-
Enthesitis	12 (16.00%)	-	-
Inflammatory waist pain	18 (24.00%)	-	-
Myositis	3 (4.00%)	-	-

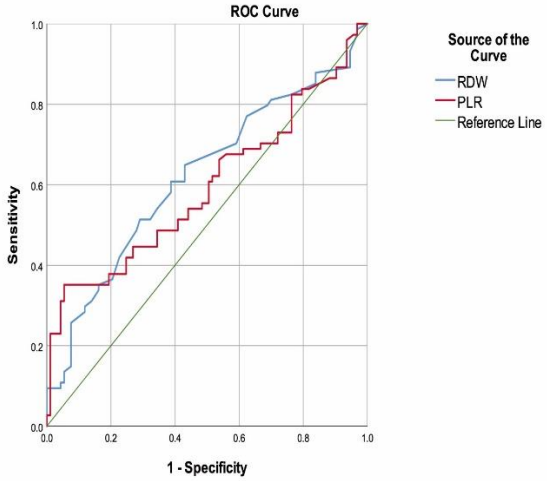
Data are given as mean (standard deviation) or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Table 2: Performance of RDW and PLR to discriminate patients with sarcoidosis and healthy controls

	RDW	PLR
Cut-off	≥14	≥171
Sensitivity	51.35%	36.00%
Specificity	70.97%	94.62%
Accuracy	62.28%	68.45%
PPV	58.46%	84.38%
NPV	64.71%	64.71%
AUC (95.0% CI)	0.621 (0.533 - 0.708)	0.599 (0.509 - 0.688)
***P*-value**	**0.007**	**0.028**

AUC: Area under ROC curve, CI: Confidence intervals, NPV: Negative predictive value, PLR: Platelet-to-lymphocyte ratio, PPV: Positive predictive value, RDW: Red cell distribution width

Figure 1: ROC curve of the RDW and PLR to discriminate patients with sarcoidosis and healthy controls



PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width, ROC: Receiver Operating Characteristic

Table 3: Correlation between SII, PIV, other hematologic parameters and clinical findings in patients with sarcoidosis

		PCT	MPV	RDW	NLR	MLR	PLR	SII	PIV
Smoking status, Smoker	r	-0.169	0.169	0.022	**0.227**	0.166	0.042	0.132	0.136
	P	0.150	0.150	0.850	**0.049**	0.156	0.721	0.260	0.246
Erythrocyte sedimentation rate	r	**0.328**	-0.082	**0.574**	**0.273**	**0.299**	**0.305**	**0.403**	**0.439**
	P	**0.006**	0.499	**<0.001**	**0.021**	**0.011**	**0.010**	**<0.001**	**<0.001**
CRP	r	0.158	-0.074	**0.264**	**0.393**	**0.319**	**0.335**	**0.483**	**0.477**
	P	0.187	0.540	**0.025**	**0.001**	**0.006**	**0.004**	**<0.001**	**<0.001**
Calcium	r	0.127	-0.139	-0.011	-0.205	-0.193	-0.098	-0.126	-0.108
	P	0.287	0.244	0.924	0.082	0.103	0.407	0.286	0.363
Stage	r	0.168	0.141	0.129	0.144	0.196	-0.067	0.140	**0.294**
	P	0.153	0.230	0.273	0.218	0.092	0.567	0.231	**0.010**
Erythema nodosum	r	-0.077	**0.308**	-0.041	**-0.319**	**-0.280**	-0.186	**-0.293**	**-0.280**
	P	0.515	**0.008**	0.730	**0.005**	**0.015**	0.109	**0.011**	**0.015**
Uveitis	r	**-0.277**	-0.065	-0.218	0.006	-0.114	-0.099	-0.170	**-0.257**
	P	**0.017**	0.584	0.063	0.959	0.329	0.397	0.145	**0.026**
Neurosarcoidosis	r	0.026	-0.117	-0.069	0.089	0.027	0.040	0.148	0.141
	P	0.823	0.319	0.557	0.448	0.817	0.736	0.205	0.228
Ankle arthritis	r	-0.092	-0.086	0.062	-0.052	0.008	0.064	-0.064	-0.131
	P	0.434	0.464	0.598	0.656	0.947	0.585	0.585	0.264
Other arthritis	r	0.043	0.059	0.093	-0.048	-0.090	0.053	0.015	-0.045
	P	0.715	0.620	0.431	0.682	0.442	0.654	0.898	0.701
Arthralgia	r	-0.062	-0.059	0.135	0.149	0.140	0.144	0.106	0.037
	P	0.602	0.618	0.251	0.202	0.232	0.219	0.366	0.755
Dactylitis	r	0.061	-0.010	-0.181	**-0.255**	-0.211	**-0.251**	-0.167	-0.069
	P	0.606	0.935	0.122	**0.028**	0.070	**0.030**	0.153	0.556
Enthesitis	r	0.027	0.013	-0.009	-0.190	-0.190	-0.101	-0.111	-0.163
	P	0.822	0.913	0.936	0.103	0.103	0.390	0.344	0.162
Inflammatory waist pain	r	0.037	-0.006	0.078	-0.085	-0.042	0.036	-0.035	-0.059
	P	0.755	0.960	0.508	0.468	0.722	0.759	0.768	0.614
Myositis	r	0.108	0.074	0.011	**-0.248**	-0.226	-0.176	-0.151	-0.132
	P	0.362	0.531	0.924	**0.032**	0.051	0.131	0.196	0.259

CRP: C-reactive protein, MLR: Monocyte-to-lymphocyte ratio, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin, PIV: Pan-immune-inflammation value, PLR: Platelet-to-lymphocyte ratio, r: Spearman correlation coefficient, RDW: Red cell distribution width, SII: Systemic immune-inflammation index

Discussion

To diagnose sarcoidosis, it is necessary to confirm the presence of granulomas in the lung or other tissues using invasive techniques such as biopsy or bronchoalveolar lavage. Once granulomas are detected, it is also crucial to exclude other diseases that share similar clinical or histopathological features to establish a diagnosis [13]. However, despite such meticulous efforts, the diagnosis can only be described as "near-conclusive" [6]. These challenges in sarcoidosis diagnosis (and ultimately management) could potentially be resolved by incorporating specific biomarkers into clinical practice for both diagnostic and prognostic purposes. Unfortunately, universally accepted biomarkers are not yet available to help diagnose or evaluate sarcoidosis [11].

In this study, we investigated the relationship of various biomarkers, including PIV and SII, with the diagnosis and clinical features of sarcoidosis. We found that patients with sarcoidosis had a lower absolute lymphocyte count, and higher RDW, ESR, and PLR than the control group. A significant weak positive correlation was found between PIV and disease stage, as well as between MPV and the presence of erythema nodosum. We also identified other correlations between sarcoidosis-related features and the examined parameters, but they were too weak to be notable.

It is increasingly evident that specific inflammatory pathways play a crucial role in the progression and outcomes of various diseases [33–35]. Immune system overactivation is believed to be a key factor in the pathogenesis of sarcoidosis. As the role of inflammation in pathogenesis becomes clearer, identifying potential biomarkers for managing sarcoidosis becomes even more important [10]. Numerous serum, bronchoalveolar lavage fluid, and radiological parameters have been studied as diagnostic and prognostic markers in sarcoidosis. However, Kraaijvanger et al. [4] reported a common limitation of these serum biomarkers, namely their low sensitivity and specificity for diagnosis. In our study, we observed that SII and PIV had no diagnostic role in sarcoidosis. Patients with sarcoidosis exhibited lower lymphocyte levels and significantly higher RDW, ESR, and PLR levels than healthy individuals. However, RDW and PLR performed poorly in distinguishing between patients with sarcoidosis and controls. Some studies have reported a higher incidence of leukopenia and lymphopenia in patients with sarcoidosis [36,37]. Additionally, other studies have demonstrated significantly higher levels of RDW [38,39], PLR [40,41], NLR [12,42], MPV [24,42], CRP [13,43] and ESR [43] in patients with sarcoidosis compared to healthy subjects. A review published in 2019 identified soluble interleukin-2 receptors, CRP, serum amyloid A, and chitotriosidase as the most effective markers for confirming sarcoidosis (highest sensitivity), while angiotensin-converting enzyme (ACE), gammaglobulins, and lysozyme exhibited the highest specificity values for ruling out sarcoidosis [13].

Kobak et al. [9] proposed that adipokines might play a significant role in granuloma formation in sarcoidosis by stimulating the Th1 response and activating various inflammatory cells. In their study, they investigated serum adipokines and their potential associations with disease activity or clinical phenotype in patients with sarcoidosis. They found that serum adiponectin levels, an anti-inflammatory protein, were higher in patients with sarcoidosis than healthy subjects, while serum leptin levels were similar to controls. The authors emphasized the potential role of adiponectin in the benign nature, self-limitation, and certain clinical features of sarcoidosis. Although sarcoidosis is generally benign and self-limiting, with spontaneous remission occurring at times, approximately one-third of patients develop chronic inflammation, pulmonary fibrosis, or irreversible damage to other organs [4,12,44]. Therefore, a comprehensive understanding of the pathogenesis of sarcoidosis and the role of immune responses is crucial [10]. Clarifying the relationship between the immune system and the pathogenesis of sarcoidosis would not only contribute significantly to diagnosing sarcoidosis and predicting prognosis but also aid in the development of new treatment strategies. Despite significant changes reported in the levels of several biomarkers in patients with sarcoidosis compared to healthy subjects, a specific marker exclusive to sarcoidosis has yet to be identified. Our data on SII and PIV also yielded similar results, suggesting that these indexes do not have a diagnostic role. Nevertheless, further comprehensive studies are needed to support the results of this study.

The formation of granulomas in the affected organs of patients with sarcoidosis is considered a significant complication. Typically, granulomas are localized in the lungs, mediastinal and peripheral lymph nodes, skin, eyes, and liver, while vital organs such as the heart and central nervous system are rarely affected [44]. The etiopathogenesis of granulomas remains unknown [10]. Due to the variable manifestations of sarcoidosis, our current understanding does not allow for predicting the extent, progression, and response to therapy in patients [4,11].

In our study, we observed a weak positive correlation between PIV and the lung stage of sarcoidosis, as well as between MPV and erythema nodosum. Several studies in patients with sarcoidosis have reported significant associations between lymphopenia and severe visceral involvement [45], extrathoracic disease [46], higher disease activity [47], worse prognosis [36,37], more severe disease [37], sarcoid uveitis [37], and sarcoid myelitis [48]. One study found a correlation between serum adiponectin levels and arthralgia and ankle swelling [9]. Another study showed a higher frequency of high NLR in patients with extrapulmonary involvement [42]. Bekir et al. [25] demonstrated that lymphocyte count was significantly lower in the chronic group upon admission, while NLR was significantly higher in the chronic group compared to the remitting sarcoidosis group, suggesting a possible association between lymphocyte count, NLR levels, and prognosis. A review reported that tumor necrosis factor alpha and chemokine ligand 18 might help identify patients at high risk of developing pulmonary fibrosis or progressive disease [13]. In a different study, an NLR level greater than 35 was associated with pulmonary hypertension in patients with sarcoidosis [49]. Karataş et al. [38] found that stage II patients had significantly higher RDW compared to those with stage I disease, suggesting that serial RDW levels might be useful in predicting disease progression [50]. While serum ACE levels have been found to be elevated in 30–80% of sarcoidosis patients, their sensitivity for diagnosis ranges from 22% to 86%, and their specificity ranges from 54% to 95% [13]. Despite this

poor predictive performance, another study reported that elevated serum ACE levels before treatment were significantly associated with improved lung function after 6 months of methotrexate treatment [51]. Despite the wealth of research on prognostic markers, there is a lack of high-performance predictors associated with the severity, stage, extent, treatment response, and prognosis of sarcoidosis. Further studies are necessary to identify inflammatory markers that can be utilized in patients with sarcoidosis, even if they can only be applied to select patients.

Limitations

This study represents the first investigation into the relationship between SII and PIV and the diagnosis, severity, and extent of sarcoidosis. However, it is important to consider several limitations when interpreting the findings. First, the study had a retrospective, single-center design and a relatively small sample size, which can be attributed to the rarity of the disease. Consequently, it is challenging to generalize the results to broader populations. Additionally, the study only assessed patient parameters at the time of diagnosis without evaluating longitudinal changes in these variables. As a result, the study did not explore the association between these parameters and treatment response, prognosis, or mortality, nor did it provide information on follow-up times and disease duration. While efforts were made to exclude potential influencing factors, some patient data may have been omitted or not recorded, introducing potential bias. Nonetheless, this limitation applies to all studies examining these inflammatory parameters, and our exclusion of recent infections and comorbidities would have minimized the number of confounding variables. Finally, the study did not consider recent medication information; however, given the exclusion criteria, this particular limitation is likely to have had a minimal impact on the results.

Conclusions

In summary, the study findings indicated that PIV and SII values in patients with sarcoidosis did not significantly differ from those of healthy individuals. Only a weak positive correlation was observed between PIV and lung stage, as well as between MPV and erythema nodosum. The study also revealed that low lymphocyte counts and high RDW, PLR, and ESR were associated with sarcoidosis diagnosis. Although the predictive performance of these parameters was limited, they are readily available and cost-effective, suggesting potential value for clinicians in terms of diagnosis, prognosis, or management. Further comprehensive studies are necessary to better understand the roles of SII, PIV, and other markers in sarcoidosis diagnosis and determination of its extent.

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