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Original Article

Evaluation of inflammatory markers in the diagnosis, differential diagnosis, and prognosis of pulmonary sarcoidosis

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ABSTRACT

Aims: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and prognostic nutritional index (PNI) are practical and readily available laboratory markers that provide valuable information regarding the diagnosis, disease severity, and prognosis of various inflammatory conditions. This study aimed to evaluate the diagnostic and prognostic utility of these inflammatory indices (NLR, PLR, LMR, SII, CAR, and PNI) in patients with pulmonary sarcoidosis.

Methods: This retrospective study included 107 patients diagnosed with sarcoidosis and 103 healthy control subjects who were evaluated at Şişli Etfal Training and Research Hospital between November 15, 2019, and November 15, 2024. Demographic characteristics, radiological findings, disease stages, and baseline laboratory parameters-including neutrophil, lymphocyte, platelet counts, C-reactive protein, and albumin levels-were recorded. The inflammatory indices were calculated, and statistical and regression analyses were performed to assess their diagnostic and prognostic significance.

Results: The study population consisted of 107 patients with pulmonary sarcoidosis and 103 healthy controls. A statistically significant difference in PNI values was observed among different disease stages in the patient group ($F=7.099$, $p<0.01$). Pairwise comparisons revealed significant differences in PNI values between stage 1 and stage 2 ($p<0.05$), stage 2 and stage 3 ($p<0.01$), and stage 2 and stage 4 ($p<0.05$). CAR values also differed significantly across disease stages ($H=18.286$, $p<0.01$). Additionally, PNI values were significantly lower in patients with poor prognosis compared to those with good prognosis ($t=2.966$, $p<0.01$).

Conclusion: Inflammatory indices derived from routine laboratory parameters demonstrate diagnostic and stage-related associations in pulmonary sarcoidosis. Among these markers, PNI was the only inflammatory index independently associated with poor prognosis, suggesting that nutritional-inflammatory status may provide additional prognostic information in clinical practice.

Keywords: Pulmonary sarcoidosis, inflammation, prognosis, prognostic nutritional index, Neutrophil-to-lymphocyte ratio

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by noncaseating granuloma formation resulting from an exaggerated immune response to unidentified antigens. The disease most commonly affects the lungs and intrathoracic lymph nodes, although extrapulmonary involvement is frequently observed and contributes significantly to disease heterogeneity and prognosis.[1,2] The clinical course ranges from spontaneous remission to chronic progressive disease with pulmonary fibrosis, underscoring the need for reliable biomarkers that reflect inflammatory burden and disease activity.[1]

The immunopathogenesis of sarcoidosis is driven by dysregulated interactions between activated macrophages, monocytes, and T lymphocytes, leading to persistent granulomatous inflammation. This process is accompanied by systemic inflammatory activation and increased production of proinflammatory cytokines and acute-phase reactants.[2,3] In granulomatous and chronic inflammatory diseases, such immune activation is known to influence circulating leukocyte subsets, platelet activation, and nutritional-inflammatory balance, which can be quantified using composite inflammatory indices derived from routine laboratory tests.[3-6]

In recent years, inflammation-based indices such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and prognostic nutritional index (PNI) have gained increasing attention as accessible markers reflecting systemic inflammation and immune-nutritional status. These indices have demonstrated diagnostic and prognostic relevance in various chronic inflammatory and immune-mediated disorders, including granulomatous diseases.[3]

Several previous studies have investigated selected inflammatory markers in sarcoidosis. Elevated levels of

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classical biomarkers such as angiotensin-converting enzyme, soluble interleukin-2 receptor, interleukin-18, and C-reactive protein have been associated with disease activity and organ involvement.[3-5] However, these biomarkers are not always routinely available and may lack sufficient specificity for clinical decision-making. More recently, hematological indices such as NLR and PLR have been evaluated in sarcoidosis, with studies reporting associations with radiological stage, extrapulmonary involvement, and prognosis.[6-8] Nevertheless, the results remain inconsistent, and most studies have focused on a limited number of indices without comprehensive evaluation across disease stages and outcomes.[3,5-8]

Importantly, there is a paucity of data simultaneously assessing multiple inflammation-based indices-including SII, CAR, and PNI-in patients with newly diagnosed pulmonary sarcoidosis, particularly in relation to radiological staging and clinical prognosis.[6-8] The potential role of combined inflammatory and nutritional indices in reflecting disease severity and predicting outcomes in sarcoidosis therefore remains insufficiently defined.[3-6]

Accordingly, the primary aim of this study was to evaluate the diagnostic value of systemic inflammatory indices in distinguishing patients with newly diagnosed pulmonary sarcoidosis from healthy controls. The secondary aim was to investigate the associations of these indices with radiological disease stages and clinical prognosis, thereby addressing an important gap in the existing literature and exploring their potential utility as practical biomarkers in clinical assessment and risk stratification.[5,6-8]

METHODS

Ethics

The study was conducted with the permission of the Clinical Researches Ethics Committee of Şişli Hamidiye Eftal Training and Research Hospital (Date: 03.12.2024, Decision No: 2840). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study was designed as a single-center, retrospective cohort study conducted at the Chest Diseases Outpatient Clinics of Şişli Hamidiye Eftal Training and Research Hospital. Medical records of patients evaluated between November 15, 2019, and November 15, 2024, were systematically reviewed. Adult patients with a definitive diagnosis of sarcoidosis were included based on compatible clinical manifestations, radiological findings, and histopathological confirmation, in accordance with established diagnostic criteria. A control group of individuals without sarcoidosis was included to assess the diagnostic value of systemic inflammatory indices. Due to the retrospective nature of the study, no additional diagnostic or therapeutic interventions were performed. All laboratory analyses, imaging studies, pulmonary function tests, and clinical assessments were conducted as part of routine clinical care at the time of diagnosis and during standard outpatient follow-up.

The primary objective of the study was to evaluate the diagnostic and prognostic significance of baseline systemic inflammatory indices measured at the time of diagnosis. Accordingly, inflammatory indices were compared between patients with and without sarcoidosis, and their associations with disease severity, radiological stage, and clinical outcomes were analyzed. Follow-up data were obtained from outpatient clinic visits and electronic medical records, allowing longitudinal assessment of disease course. This retrospective observational design enabled the evaluation of real-world clinical data without influencing patient management.

Clinical prognosis was predefined prior to analysis and categorized as poor or favorable based on objective criteria assessed during follow-up. Poor prognosis was defined by the presence of one or more of the following: need for systemic therapy (systemic corticosteroids and/or immunosuppressive agents) due to disease progression or persistent symptoms; radiological progression, including worsening radiological stage or development of new parenchymal or fibrotic changes; or a ≥10% relative decline in forced vital capacity (FVC) compared with baseline. Patients who did not meet these criteria and remained clinically stable or showed improvement during follow-up were classified as having a favorable prognosis. The predefined follow-up duration was 24 months after diagnosis.

Study Population

The study population consisted of patients with sarcoidosis and healthy control subjects.

Sarcoidosis Group

The sarcoidosis group included 107 patients with a definitive diagnosis of sarcoidosis established through compatible clinical findings, radiological features, and histopathological confirmation.

Control Group

The control group consisted of 103 healthy individuals with complete baseline laboratory data, selected from individuals attending outpatient clinics or health screening programs. Participants in the control group had no history of sarcoidosis or other inflammatory, autoimmune, malignant, or chronic systemic diseases that could affect systemic inflammatory parameters. None were receiving systemic corticosteroids, immunosuppressive agents, or anti-inflammatory treatments at the time of enrollment.

Inclusion and Exclusion Criteria

Participants aged ≥18 years with available baseline laboratory data and documented informed consent were eligible for inclusion. To minimize confounding related to systemic inflammation, pregnant women and individuals with malignancy, metabolic disorders, rheumatologic diseases, vasculitis, inflammatory bowel disease, hematological disorders, chronic kidney disease, autoimmune diseases, cardiovascular disease, chronic lung diseases, or other serious comorbid conditions were excluded.

Data Collection and Laboratory Measurements

Demographic and clinical data were retrospectively obtained from electronic medical records of the patients. Data regarding age, sex, posteroanterior (PA) chest X-ray and thoracic computed tomography (CT) findings, hemoglobin, serum albumin and CRP levels, neutrophil, lymphocyte, monocyte, and platelet counts, radiological stage of sarcoidosis, pulmonary function test parameters, extrapulmonary involvement, treatment requirements, and

clinical course during follow-up were recorded. Baseline systemic inflammatory indices-including NLR, LMR, PLR, SII, CAR, PNI-were calculated using standard formulas derived from laboratory parameters obtained at the time of diagnosis.

The inflammatory indices were calculated as follows: NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count; LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count; PLR was defined as the platelet count divided by the lymphocyte count; SII was calculated using the formula platelet count×neutrophil count/lymphocyte count; CAR was calculated as serum C-reactive protein level divided by serum albumin level; and PNI was calculated as serum albumin (g/L)+5× total lymphocyte count (10^9/L). These formulas are widely accepted and have been previously validated as reliable indicators of systemic inflammation and nutritional status in chronic inflammatory and granulomatous diseases. The inflammatory indices were calculated using standard and previously validated formulas as described in the literature.[6,7,9,10]

Radiological Staging

Patients with sarcoidosis were radiologically staged according to standard chest X-ray classification into five categories: stage 0, normal chest radiograph; stage 1, bilateral hilar lymphadenopathy; stage 2, bilateral hilar lymphadenopathy with pulmonary parenchymal involvement; stage 3, pulmonary parenchymal involvement without hilar lymphadenopathy; and stage 4, pulmonary fibrosis.

Statistical Analysis

Patient data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows 29.0 (IBM Corp., Armonk, NY). Frequency and percentage values for categorical and mean and standard deviation for continuous data were given as descriptive values. For comparisons between two groups, the independent sample t-test was used, and the Pearson' chi-square test was used to compare categorical variables. The specificity and sensitivity of the study results were evaluated via ROC analysis. Univariable analyses were performed to evaluate the association between each clinical and laboratory variable and poor prognosis in patients with sarcoidosis.

Univariable logistic regression models were constructed for the statistical evaluation of demographic characteristics, smoking exposure, radiological stage, extrapulmonary involvement. Baseline CRP levels, and systemic inflammatory indices, including NLR, LMR, PLR, SII, CAR, and PNI. odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each variable. Variables demonstrating clinical relevance and/or a p-value <0.10 in univariable analyses were considered candidates for inclusion in multivariable models. Multivariable logistic regression analysis was performed to identify independent predictors of poor prognosis in patients with sarcoidosis. A parsimonious multivariable model was constructed by including variables with clinical significance and those meeting the predefined statistical threshold in univariable analysis. Adjusted odds ratios with 95% CIs were reported. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The study population consisted of 210 participants, including 107 patients with pulmonary sarcoidosis and 103 healthy control subjects (**Figure**). Sarcoidosis group comprised 73 (68.2%) female and 34 (31.8%) male patients, while the control group consisted of 57 (55.3%) female and 46 (44.7%) male participants without any statistically significant intergroup difference in terms of gender distribution (p=0.055). The mean age was 51.87 years in the sarcoidosis group and 51.67 years in the control group, without any significant intergroup difference (p=0.925) (**Table 1**). Patients with sarcoidosis demonstrated significantly altered inflammation-based indices compared with controls, reflecting a higher systemic inflammatory burden at the time of diagnosis.

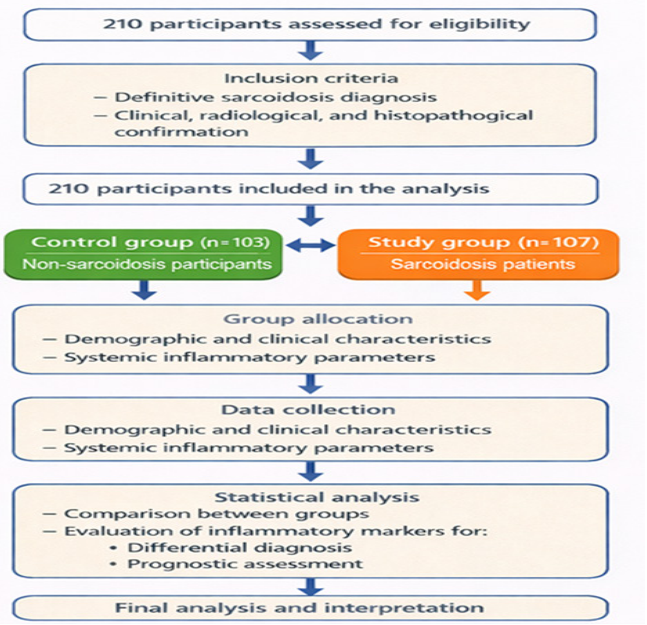

Figure. Flowchart of patient selection and study design

Compared with the control group, patients with sarcoidosis exhibited significantly lower hemoglobin (Hb) and hematocrit (HCT) levels (p=0.042 and p=0.038, respectively). Additionally, significant differences were identified between the two groups regarding alkaline phosphatase (ALP), albumin, CRP, and all evaluated inflammatory indices, including NLR, LMR, PLR, CAR, PNI, and SII (all p<0.01) (**Table 2**).

When inflammatory indices of the patients with sarcoidosis were analyzed according to radiological stages, a statistically significant difference was observed for PNI values (F=7.099, p<0.01). Post-hoc analysis with Tukey correction revealed significant differences between stages 1 and 2 (p=0.041), stages 2 and 3 (p<0.01), and stages 2 and 4 (p=0.015). Similarly, LMR values differed significantly across radiological stages (H=9.816, p=0.02), mainly driven by differences observed between stage 2 and stage 3 (p=0.007) and between stages 2 and 4 (p=0.026). CAR values also showed significant variation among stages (H=18.286, p<0.01), primarily due to differences between stage 1 and stage 2 (p<0.01) and between stage 2 and stage 3 (p=0.001). No statistically significant stage-related differences were observed for NLR, PLR, or SII (**Tables 2 and 3**). Regarding clinical prognosis, PNI values were significantly lower in patients with a poor prognosis than in those with a favorable prognosis (p=0.004). No significant correlations

were detected between prognosis and NLR, LMR, PLR, CAR, or SII values (Table 4).

Table 1. Comparison of study groups in terms of demographic characteristics, hematological parameters, and inflammatory markers

Variables	Study group (n=107)	Control group (n=103)	p-value
Gender n (%)			0.055[3]
Female	73 (68.2)	57 (55.3)	
Male	34 (31.8)	46 (44.7)	
Age	51.87±15 (23-87)	51.67±15.8 (19-81)	0.925[1]
Albumin (g/L)	41.9 (32.1-51)	43.2 (31.7-50.2)	0.0001**[2]
White blood cell ($x10^9$/L)	6.8 (3.41-12.91)	7.29 (4.52-10.9)	0.204[2]
Neutrophil ($x10^9$/L)	4.39 (1.89-11.15)	4.2 (0.39-9.29)	0.169[2]
Lymphocyte ($x10^9$/L)	1.64 (0.24-4.2)	2.22 (0.98-4.4)	0.0001**[2]
Platelet ($x10^9$/L)	265 (100-533)	252 (150-433)	0.289[2]
Monocyte ($x10^9$/L)	0.51 (0.12-1.2)	0.4 (0.2-2.3)	0.002**[2]
C-reactive protein (mg/L)	8.14 (0.3-198)	2.06 (0.1-8)	0.0001**[2]
NLR	1.89 (0.99-14.22)	1.39 (-9.38- 3.63)	0.0001**
LMR	3.39 (0.49-25.58)	5.23 (1-12.47)	0.0001**
PLR	152.9 (74.9-825)	116.84 (51.14-300)	0.0001**
CAR score	0.199 (0.007-6)	0.048 (0.002-0.178)	0.0001**
PNI	41.91 (32.11-51.01)	43.21 (31.71-50.21)	0.0001**
SII index	649.03 (268.46-8563.5)	500.63 (58.03-1716.8)	0.0001**

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index. [1]: Analysis of Variance ANOVA; [2]: Kruskal- Wallis test; *: p<0.05; **: p<0.01; Parameters indicated with *, **, **2 are represented as median (min-max) values

ROC analyses demonstrated that all evaluated inflammatory indices had statistically significant discriminatory ability for sarcoidosis. The optimal cut-off values, sensitivities, and specificities were as follows: NLR, cut-off 1.54 (sensitivity 65.4%, specificity 65.0%); LMR, cut-off 4.47 (sensitivity 71.8%, specificity 72.0%); PLR, cut-off 133.82 (sensitivity 68.2%, specificity 68.0%); CAR, cut-off 0.0805 (sensitivity 72.9%, specificity 73.8%); PNI, cut-off 42.57 (sensitivity 64.1%, specificity 64.5%); and SII, cut-off 559.99 (sensitivity 62.6%, specificity 62.3%). All ROC analyses were statistically significant (p<0.01) (Table 5).

Table 4. Comparison of inflammatory markers according to prognosis in study groups

Inflammation markers	Poor prognosis (n=55)	Improvement (n=52)	p-value
	Mean±SD	Mean±SD	
PNI	42.16±3 (32.4-51.01)	40.37±3.3 (32.11-47.01)	0.004**[1]
	(Min-max)	(Min-max)	
NLR	1.93 (1.07-4.75)	1.795 (0.99-14.22)	0.62[2]
LMR	3.61 (1.09-25.58)	2.91 (0.49-9)	0.06[2]
PLR	147.95 (74.9-383.12)	169.175 (76.28-825)	0.243[2]
CAR score	0.141 (0.01-2.421)	0.23 (0.007-6)	0.331[2]
SII	633.46 (294.13-2120.7)	678.79 (268.46-8563.5)	0.184[2]

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, Min: Minimum, Max: Maximum. [1]: Independent samples t test; [2]: Mann- Whitney U test; **: p<0.01

Comparison of Inflammatory Indices Between Sarcoidosis and Control Groups and Prognostic Analyses

In univariable logistic regression analyses, several clinical and laboratory parameters-including age, smoking burden, radiological stage, extrapulmonary involvement, CRP, and all evaluated inflammation-based indices (NLR, LMR, PLR, SII, CAR, and PNI)-were significantly associated with poor prognosis in patients with sarcoidosis (Table 6). However, after adjustment for potential confounders (age, sex, radiological stage, extrapulmonary involvement, smoking status, and CRP) in multivariable analysis, only PNI remained independently

Table 2. Comparison of inflammatory markers according to stages of sarcoidosis in the study groups

Inflammatory markers	Stage 1 n=18	Stage 2 n=42	Stage 3 n=30	Stage 4 n=17	p-value
PNI mean±SD	41.92±2.3 (36.01-45.51)	39.66±3.5 (32.11-47.01)	42.64±2.8 (38.01-51.01)	42.28±2.5 (37.01-46.01)	0.0001**[1]
NLR (min-max)	1.735 (1.08-5.62)	2.04 (0.99-14.22)	1.805 (1.07-4.75)	1.93 (1.24-4.21)	0.676[2]
LMR (min-max)	4.06 (1.29-7.57)	2.785 (0.49-9)	4.285 (1.78-11.09)	3.61 (1.57-25.58)	0.02*[2]
PLR (min-max)	157.925 (76.28-331.58)	173.995 (77.14-825)	140.8 (74.9-274.74)	134.41 (75.56-305.38)	0.124[2]
CAR score (min-max)	0.131 (0.007-0.466)	0.307 (0.01-6)	0.102 (0.01-2.063)	0.209 (0.016-0.946)	0.0004**[2]
SII (min-max)	678.79 (307.7-2811.73)	826.16 (268.46-8563.5)	631.32 (316.4-1994.63)	540.37 (294.13-1947.97)	0.154[2]

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, Min: Minimum, Max: Maximum. [1]: Analysis of Variance ANOVA; [2]: Kruskal-Wallis test; *: p<0.05; **: p<0.01; Parameters PNI, and PLR are indicated as median (min-max) values, while the other parameters are srepresented as mean ±SD (min-max) values

Table 3. Investigation of the effect of inflammatory markers on sarcoidosis by logistic regression analysis

Sarcoidosis		B	SE	Wald	SD	p-value	Exp (B)
Inflammatory markers (NLR, LMR, PLR, CAR score, PNI, SII)	NLR	-0.946	0.489	3.734	1	0.053	0.388
	LMR	0.077	0.074	1.081	1	0.298	1.080
	PLR	-0.014	0.007	4.497	1	0.034*	0.986
	CAR score	-18.950	3.626	27.310	1	0.0001**	0.000
	PNI	-0.015	0.070	0.048	1	0.827	0.985
	SII	0.002	0.001	1.853	1	0.173	1.002
	Constant	4.584	3.277	1.957	1	0.162	97.935

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index. NLR, LMR, PLR, CAR Score, PNI, and SII simultaneously significantly affect Sarcoidosis. (Logistic Regression Analysis; p<0.001)

Table 5. Results of ROC analysis for inflammatory markers according to prognosis in study groups

Cut-off value for NLR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
NLR	0,709 (0,639;0,778)	1,54	0,0001**	65,40%	65,00%
Cut-off value for LMR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
LMR	0.75 (0.684; 0.816)	4.47	0.0001**	71.80%	72.00%
Cut-off value for PLR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
PLR	0.724 (0.656; 0.791)	133.815	0.0001**	68.20%	68.00%
Cut-off value for CAR score					
Risk faktörü sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
CAR score	0.827 (0.77; 0.884)	0.0805	0.0001**	72.90%	73.80%
Cut-off value for PNI					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
PNI	0.677 (0.605; 0.749)	42.565	0.0001**	64.10%	64.50%
Cut-off value for SII					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
SII	0.705 (0.636; 0.774)	559.985	0.0001**	62.60%	62.10%

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, AUC: Area under the curve

Table 6. Univariable logistic regression analysis for predictors of poor prognosis in sarcoidosis

Variables	OR (95% CI)	p value
Age (years)	1.03 (1.01–1.06)	0.012
Female sex	0.78 (0.41–1.49)	0.458
Smoking (pack-years)	1.02 (1.00–1.04)	0.036
Radiological stage	1.41 (1.08–1.86)	0.011
Extrapulmonary involvement	2.18 (1.16–4.10)	0.016
C-reactive protein (mg/L)	1.06 (1.02–1.10)	0.002
NLR	1.74 (1.28–2.36)	<0.001
LMR	0.71 (0.58–0.86)	<0.001
PLR	1.01 (1.00–1.02)	<0.001
SII	1.001 (1.000–1.002)	<0.001
CAR	2.63 (1.74–3.96)	<0.001
PNI	0.88 (0.82–0.94)	<0.001

CI: Confidence interval, OR: Odds Ratio, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: prognostic nutritional index

Table 7. Multivariable logistic regression analysis for poor prognosis

Variables	Adjusted OR (95% CI) median (95% CI)	p value
Age	1.02 (0.99-1.05)	0.15
Female sex	0.91 (0.45-1.86)	0.80
Radiological stage	1.29 (0.96-1.74)	0.09
Extrapulmonary involvement	1.94 (1.01-3.71)	0.047
C-reactive protein (mg/L)	1.04 (1.00-1.08)	0.041
Smoking (≤20 pack-years)	1.21 (0.62-2.35)	0.58
Smoking (>20 pack-years)	1.89 (1.01-3.56)	0.044
PNI	0.91 (0.84-0.98)	0.014

CI: Confidence interval, PNI: Prognostic nutritional index

associated with poor prognosis (adjusted OR 0.91, 95% CI 0.84-0.98; p=0.014), while extrapulmonary involvement, CRP levels, and heavy smoking (>20 pack-years) also retained prognostic significance (Table 7). Other inflammation-based indices lost statistical significance, suggesting that their apparent prognostic effects may be mediated by confounding clinical and inflammatory factors.

Regarding diagnostic discrimination, univariable analyses demonstrated that higher NLR, LMR, PLR, SII, and CAR values, along with lower PNI values, were significantly associated with the presence of sarcoidosis compared with controls (all p<0.05). In multivariable analysis, only CAR and LMR remained independently associated with sarcoidosis, whereas the other indices did not retain significance, indicating substantial overlap and possible collinearity among inflammation-based parameters derived from shared hematological components.

Association Between Inflammatory Indices and Radiological Disease Stages

Stage-based subgroup analyses demonstrated significant differences in selected inflammatory indices across radiological stages of sarcoidosis. PNI values differed significantly according to disease stage (one-way ANOVA, F=7.099; p=0.0001). Pairwise comparisons revealed that PNI values were significantly lower in stage 2 compared with stage 1 (p=0.041), stage 3 (p=0.0001), and stage 4 (p=0.015), indicating progressive impairment of nutritional-inflammatory status with advancing radiological involvement. Similarly, CAR values showed a significant variation across radiological stages (Kruskal-Wallis test, H=18.286; p=0.0004). Patients with more advanced stages exhibited higher CAR levels, reflecting increased systemic inflammation relative to albumin levels. These findings support a close association between inflammatory burden and radiological disease extent.

Prognostic Analyses and Clinical Outcomes

In univariable logistic regression analyses evaluating predictors of poor prognosis among patients with sarcoidosis (Table 6), increasing age, cumulative smoking exposure, higher radiological stage, extrapulmonary involvement, and elevated

CRP levels were significantly associated with adverse outcomes. Among inflammation-based indices, higher derived NLR, PLR, SII, and CAR were associated with an increased risk of poor prognosis, whereas higher LMR and PNI were associated with a reduced risk. Notably, NLR (OR 1.74, 95% CI 1.28-2.36), CAR (OR 2.63, 95% CI 1.74-3.96), and PNI (OR 0.88, 95% CI 0.82-0.94) demonstrated the strongest univariable associations with prognosis (all p<0.001). In multivariable logistic regression analysis (**Table 7**), extrapulmonary involvement (adjusted OR 1.94, p=0.047), CRP levels (adjusted OR 1.04, p=0.041), smoking exposure greater than 20 pack-years (adjusted OR 1.89, p=0.044), and PNI (adjusted OR 0.91, p=0.014) remained independently associated with poor prognosis. PNI consistently emerged as an independent protective factor, underscoring the prognostic relevance of nutritional-inflammatory status in sarcoidosis.

Subgroup and Pairwise Analyses

When patients were stratified according to radiological stage, significant differences were observed in systemic inflammatory indices. PNI values progressively decreased with advancing radiological stage (p<0.01), with post-hoc analyses revealing significant differences between stage 1 and stage 2 (p=0.041), stage 2 and stage 3 (p<0.001), and stage 2 and stage 4 (p=0.015). Similarly, CAR and SII values increased significantly across higher radiological stages (p<0.01), indicating a stronger systemic inflammatory burden in advanced disease. In prognosis-based subgroup analyses, patients with poor prognosis exhibited significantly lower PNI values and higher CAR levels compared with those with good prognosis (p<0.01 for both), suggesting that combined inflammatory-nutritional indices may reflect disease severity and clinical outcomes.

DISCUSSION

In this study, systemic inflammatory indices derived from routine laboratory parameters were comprehensively evaluated in patients with newly diagnosed pulmonary sarcoidosis. The main findings demonstrate that several inflammation-based indices differ significantly between sarcoidosis patients and healthy controls and that selected indices are associated with radiological disease stage and clinical prognosis. These results support the concept that sarcoidosis is characterized by persistent systemic immune activation extending beyond localized granulomatous inflammation.[3,11] These observations indicate that sarcoidosis is not merely a localized granulomatous disorder confined to affected organs, but rather a condition characterized by sustained systemic immune activation and dysregulated inflammatory responses.[3,11,12]

Granuloma formation in sarcoidosis is driven by complex interactions between activated macrophages, T lymphocytes, and pro-inflammatory cytokines, processes that are known to influence circulating leukocyte subsets, platelet activation, and acute-phase reactants.[13-15]

Consequently, composite inflammatory indices such as NLR, LMR, CAR, SII, and PNI may reflect the global inflammatory burden and immune–nutritional imbalance associated with disease activity and progression. Previous studies have reported alterations in hematological and inflammatory profiles in patients with sarcoidosis; however, the majority of these investigations have primarily focused on single inflammatory markers or a limited number of indices. Moreover, these studies have often evaluated diagnostic associations in isolation, without comprehensively examining the simultaneous relationships between multiple inflammation-based indices, radiological disease staging, and longitudinal clinical outcomes. As a result, the integrated prognostic value of routinely available composite inflammatory indices in sarcoidosis remains insufficiently characterized.[16,17]

Neutrophil- and platelet-based indices, including NLR, LMR, and PLR, were significantly altered in the sarcoidosis group compared with controls, indicating an underlying systemic inflammatory response. Similar alterations in leukocyte-derived ratios have been reported in previous studies on sarcoidosis and other granulomatous lung diseases, reflecting enhanced innate immune activity and relative lymphocyte suppression.[6,18] However, consistent with more recent reports, these indices did not reliably distinguish radiological stages or prognostic subgroups in our cohort.[19] This suggests that while NLR, LMR, and PLR may be useful markers of systemic inflammation, their ability to reflect disease severity or long-term outcome in sarcoidosis is limited.

The CAR score demonstrated a strong association with both radiological stage and sarcoidosis diagnosis in multivariable analysis. CAR integrates CRP, a marker of acute-phase inflammatory response, with serum albumin, which reflects chronic inflammation and nutritional status. Recent studies have highlighted the prognostic value of CAR in chronic inflammatory and interstitial lung diseases, emphasizing its ability to capture both inflammatory burden and systemic catabolic state.[20,21] Our findings extend these observations to pulmonary sarcoidosis, suggesting that CAR may represent a sensitive and practical biomarker for disease activity and severity assessment at diagnosis. In contrast to leukocyte-based ratios, CAR remained independently associated with both radiological stage and disease diagnosis after multivariable adjustment, suggesting a closer relationship with the underlying inflammatory activity of sarcoidosis. Given that sarcoidosis is characterized by persistent granulomatous inflammation and systemic acute-phase responses, CAR may better capture disease-related inflammatory burden than indices derived solely from circulating blood cell counts.[22-24]

PNI was another index that showed significant differences across radiological stages and prognosis subgroups, with lower PNI values observed in patients with poorer outcomes. PNI reflects the interaction between immune competence and nutritional status, both of which are increasingly recognized as determinants of disease progression in chronic inflammatory conditions. Previous studies have demonstrated the prognostic relevance of PNI in chronic lung diseases and systemic inflammatory disorders, and our results suggest a similar role in sarcoidosis, where chronic inflammation and immune dysregulation may contribute to nutritional impairment and adverse clinical outcomes.[23,25]

Although SII values were significantly higher in sarcoidosis patients compared with healthy controls, no significant association with radiological stage or clinical prognosis was observed. This finding is consistent with recent evidence suggesting that SII primarily reflects acute systemic inflammatory responses driven by neutrophilia and thrombocytosis, rather than chronic immune dysregulation

or fibrotic disease processes.[26] Given the heterogeneous, often indolent, and sometimes self-limiting course of sarcoidosis, SII alone may therefore be insufficient to capture disease severity or predict long-term outcomes.

An important methodological consideration is that inflammation-based indices such as NLR, PLR, SII, CAR, and PNI are mathematical constructs derived from overlapping hematological and biochemical parameters. Consequently, observed correlations among these indices may partially result from numerical interdependence rather than representing independent biological pathways. This limitation has been highlighted in recent methodological and immunopathological studies, emphasizing the need for cautious interpretation of correlated composite inflammatory indices and for multivariable analyses to identify truly independent prognostic markers.[27,28]

Overall, the present study demonstrates that not all systemic inflammatory indices provide equal clinical information in pulmonary sarcoidosis. While leukocyte-derived ratios may indicate the presence of systemic inflammation, combined indices incorporating inflammatory and nutritional components-particularly CAR and PNI-appear to offer greater clinical relevance for evaluating disease severity and prognosis. These markers are inexpensive, widely available, and easily applicable in routine clinical practice, supporting their potential role as adjunctive tools in the assessment and follow-up of patients with pulmonary sarcoidosis.[23,28]

In the present study, a statistically significant variation in PNI values was observed across radiological stages of pulmonary sarcoidosis, with pairwise differences particularly evident between stage 1 and stage 2, stage 2 and stage 3, and stage 2 and stage 4. These findings suggest that nutritional and immunological status, as reflected by PNI, may deteriorate in parallel with disease progression. This observation is biologically plausible, as advanced sarcoidosis is characterized by persistent systemic inflammation, chronic immune activation, and increased metabolic demand, all of which may negatively affect serum albumin levels and lymphocyte counts.[22] Similar associations between lower PNI values and increased disease severity or worse clinical outcomes have been reported in chronic inflammatory and granulomatous diseases, supporting the role of PNI as an integrated marker of immune competence and nutritional reserve.[29]

Our findings indicate that not all inflammation-based indices provide equivalent clinical information in pulmonary sarcoidosis. Neutrophil-and platelet-derived ratios such as NLR, LMR, and PLR were significantly altered in patients compared with controls, reflecting systemic inflammatory activation; however, these indices did not reliably distinguish radiological stages or prognostic subgroups. This is consistent with previous studies reporting that leukocyte-derived ratios primarily reflect inflammatory burden rather than disease severity or long-term outcome. Differences among studies may be explained by heterogeneity in disease phenotype, extent of extrapulmonary involvement, and methodological approaches.[29,30-32]

In contrast, indices integrating inflammatory and nutritional components demonstrated greater clinical relevance. CAR varied significantly across radiological stages, supporting its role as a marker of systemic inflammatory activity, although it did not retain independent prognostic significance. Notably, PNI was the only index independently associated with prognosis, suggesting that immune-nutritional status plays a central role in long-term outcomes in sarcoidosis. This finding may reflect the impact of chronic inflammation on nutritional reserve and immune competence. Finally, given that these indices are mathematically derived from overlapping hematological parameters, observed correlations should be interpreted cautiously, as numerical interdependence may contribute to apparent associations. Overall, PNI appears to be the most robust and clinically meaningful marker for prognostic stratification in pulmonary sarcoidosis.[31,32]

Limitations

Several limitations of this study should be acknowledged. First, the retrospective and single-center design may limit the generalizability of the findings and carries an inherent risk of selection bias. Second, although inflammatory indices demonstrated statistically significant diagnostic performance, however the area under the ROC curves demonstrated mostly a modest diagnostic performance (approximately 0.65-0.75), indicating its limited discriminative ability. Therefore, these indices should not be considered definitive diagnostic or prognostic tools but rather as adjunctive markers that may complement clinical, radiological, and histopathological assessment.

Third, radiological staging in sarcoidosis does not always directly reflect inflammatory activity, as fibrotic or chronic changes may persist despite alleviated systemic inflammation. Accordingly, the associations observed between inflammatory indices and radiological stages should be interpreted with caution. Fourth, although multivariable analyses were adjusted for major confounders, residual confounding factors cannot be completely excluded. Finally, prognostic outcomes were based on clinical and radiological follow-up parameters, and longer prospective studies incorporating functional and biomarker-based endpoints are needed to validate our findings.

CONCLUSION

Sarcoidosis is a heterogeneous granulomatous disease with variable clinical outcomes ranging from spontaneous remission to chronic progression. In this study, several inflammation-based indices derived from routine laboratory parameters showed significant diagnostic and stage-related differences in patients with pulmonary sarcoidosis. However, after multivariable adjustment, the PNI was the only inflammatory marker independently associated with poor prognosis.

These findings indicate that while multiple inflammatory ratios reflect systemic inflammatory burden and disease stage, PNI may offer additional prognostic value beyond conventional clinical and radiological assessment. Therefore, PNI may serve as a practical and noninvasive adjunctive marker for risk stratification in routine clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Şişli Hamidiye Eftal Training and Research Hospital (Date: 03.12.2024, Decision No: 2840).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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