









Prognostic value of inflammatory markers determined during diagnosis in patients with sarcoidosis: chronic versus remission

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SUMMARY

OBJECTIVE: This study aimed to evaluate the prognostic value of inflammatory markers determined during admission among patients with sarcoidosis with chronic and remission groups.

METHODS: This study was designed as retrospective single-center study. Patients with sarcoidosis without treatment and who had at least two years of follow-up were included in this study. Patients were divided into two groups as chronic and remission. The primary outcome is to evaluate hematological parameters in remission and chronic sarcoidosis groups.

RESULTS: Out of 348 patients with sarcoidosis, 142 patients without treatment and followed up for at least two years were included in this study. Groups had similar demographic features with the predominance of females (80.4 and 77.9%, respectively) and stage I disease (78.6 and 68.6%, respectively). Lymphocyte count [median (IQR) 1.7 (1.3–2.3) 10⁹/L versus 2.1 (1.6–2.4) 10⁹/L, $p=0.034$] was significantly lower, whereas neutrophil to lymphocyte ratio (NLR) was significantly higher [median (IQR) 2.6 (2.0–3.1) versus 2.0 (1.6–2.8), $p=0.006$] at admission in the chronic group. No significant difference was determined in inflammatory parameters at admission between groups.

CONCLUSION: Lower lymphocyte count and higher neutrophil to lymphocyte ratio were determined in patients with chronic sarcoidosis compared with the remission group, based on monitoring of radiological staging up to five-year after the initial diagnosis. Accordingly, the identification of neutrophil to lymphocyte ratio at diagnosis seems to be a potential prognostic marker in patients with sarcoidosis beside its low cost and easy determination in routine clinical practice.

KEYWORDS: Sarcoidosis. Chronic granulomatous disease. Prognosis.

INTRODUCTION

Sarcoidosis is a systemic inflammatory granulomatous disease of unknown etiology, with pulmonary involvement in most cases, and associated with heterogeneous clinical presentation and disease course¹⁻⁴. Although a favorable outcome with

self-limiting clinics occurs in most of the patients, progression to fibrosis and thus permanent organ impairment occurs in one-third of the patients^{5,6}.

Several clinical, physiological, and radiographic parameters were under investigation for objective disease-specific biomarkers

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that can predict the severity and prognosis of sarcoidosis^{3,4,7,8}. Diagnostic and prognostic roles of inflammatory markers have been addressed by several studies in inflammatory and chronic respiratory diseases^{4,5,9-14}. Besides, limited data about serum inflammatory markers were available in the monitoring of patients with sarcoidosis^{4,5,9,13,14}.

Neutrophil to lymphocyte ratio (NLR) has been recently emerged as a cost-effective, potential inflammatory marker and found to be associated with the severity and prognosis of systemic inflammatory diseases, cancer, and respiratory and cardiac diseases. Although there are a limited number of studies, NLR was shown to be increased in patients with sarcoidosis as compared with the control group^{4,5,13,14}.

Therefore, this retrospective study was designed to evaluate the prognostic value of serum inflammatory markers [i.e., NLR, mean platelet volume (MPV), platelet/MPV ratio, angiotensin-converting enzyme (ACE), and C-reactive protein (CRP)] determined at initial diagnosis in the clinical course of disease among patients with sarcoidosis.

METHODS

Study population

Patients with sarcoidosis without treatment and who had at least 2 years of follow-up were included in this retrospective study. Patients were divided into two groups, namely, chronic and remission. Figure 1 shows the flowchart of patient enrollment.

Diagnosis of Sarcoidosis

Sarcoidosis was diagnosed as if clinical and radiological data are supported by the presence of non-caseating granulomas in a biopsy specimen, and alternative causes of granulomatous inflammation are ruled out. For patients who did not allow biopsy and/or had Löfgren syndrome, sarcoidosis was diagnosed by clinical, radiological, and laboratory compatibilities.

There are five roentgenographic stages as follows: Stage 0: normal chest X-ray; Stage 1: bilateral hilar lymphadenopathy; Stage 2: bilateral hilar lymphadenopathy together with parenchymal involvement; Stage 3: parenchymal involvement without bilateral hilar lymphadenopathy; and Stage 4: pulmonary fibrosis¹.

- *Remission*: Spontaneous clinical and radiological improvement¹⁵.
- *Chronic sarcoidosis*: Persistence of sarcoidosis more than 2 years¹⁵.
- *Extrapulmonary involvement*: The criteria specified in A Case–Control Etiologic Study of Sarcoidosis (ACCESS) trial were used for the definition of organ involvement¹⁶.
- *Hematological analysis*

Complete blood count analysis was performed *via* flow cytometry (Beckman Coulter LH 780 Analyzer; Beckman Coulter Inc., Miami, FL, USA). Serum CRP levels were determined by using the turbidimetric method using a BN II System (Siemens, Munich, Germany). ACE (U/L) was measured by using the spectrophotometric methods (EN Biochemical Enterprise, Italy). NLR was calculated by the ratio of neutrophil to lymphocyte counts. The platelet to MPV ratio was also calculated by the ratio of the platelet count to MPV.

Outcome measures

Data on patient demographics, stage of the disease, duration of follow up, and total blood count (i.e., neutrophil, lymphocyte, and thrombocyte) and inflammatory markers (i.e., ACE, CRP, MPV, NLR, and platelet/MPV ratio) determined at diagnosis were obtained from medical records in both chronic and remission groups. The percentage of survivors and non-survivors was also recorded in both groups.

Ethics

The study was approved by the Ethical Committee of the institution (05.11.2020/116.2007.197) and was in accordance with the Declaration of Helsinki. As informed consent from patients to review their medical records was not obtained, patient data were de-identified and strictly protected.

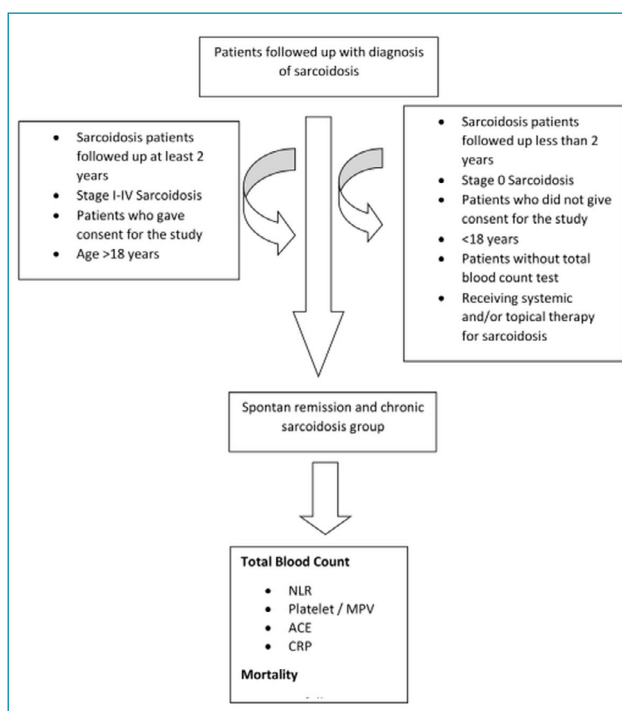


Figure 1. Flowchart of this study.

Statistical analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0, released 2012, IBM Corp., Armonk, New York, USA). Fisher's exact test and Pearson's chi-square analysis were performed for categorical variables. Mann–Whitney U test was used for comparison of numerical variables. Data were expressed as “mean (standard deviation; SD)”, “n (%)” and “median (minimum and maximum)” values, where appropriate. $p < 0.05$ was considered statistically significant.

RESULTS

Among 348 patients with sarcoidosis, 142 patients with stage I–III sarcoidosis without treatment and had at least two years of follow-up were included in this retrospective study.

Remission and chronic groups had similar demographic and sarcoidosis features with the predominance of females (80.4 and 77.9%, respectively) and Stage I disease (78.6 and 68.6%, respectively). Stage IV sarcoidosis did not exist in this study population. Extrapulmonary involvement was determined in one-third of patients in both groups. Remission occurred in 39.4% of patients (Table 1).

Patients in the remission and chronic groups had a similar duration of follow-up (median 62.5 and 60.0 months, respectively) and low mortality (0.0 and 4.7%, respectively; Table 1).

Lymphocyte count [median (IQR) 1.7 (1.3–2.3) $10^9/L$ versus 2.1 (1.6–2.4) $10^9/L$, $p = 0.034$] was significantly lower, whereas

NLR was significantly higher [median (IQR) 2.6 (2.0–3.1) versus 2.0 (1.6–2.8), $p = 0.006$] at admission in the chronic group when compared with remission group. No significant difference was noted in other inflammatory parameters between groups including ACE, CRP, MPV, and PLT/MPV ratio (Table 2).

DISCUSSION

In this study, despite the similar baseline demographic and disease characteristics, the chronic sarcoidosis group had decreased lymphocyte count and increased NLR, compared with the remission group. Lymphocyte count and NLR levels were found to indicate the prognosis in patients with sarcoidosis. Thus, patients with low lymphocyte count and high NLR values had a higher likelihood of developing chronic disease than the clinical remission.

Sarcoidosis is observed most frequently in women in different studies^{17,18}. In this study, the ratios of female patients were similar in both groups. In recent studies, the ratios of patients with stages I and II were higher in all patients with sarcoidosis, which is compatible with the literature¹⁷⁻¹⁹. In this study, patients with stage IV sarcoidosis did not exist, besides the ratio of stage II disease in the chronic group was almost two-fold greater than the remission group without statistical significance.

In recent studies, remission in sarcoidosis was reported to occur in more than half of patients within 3 years^{6,7}. In a study conducted by Scadding et al., complete radiological remission after >5-year follow-up was reported to occur in 84%, 58%,

Table 1. Demographic and disease-related characteristics in study groups.

		Remission (n=56)	Chronic course (n=86)	p-value
Age (year)	Mean (SD)	41.5 (11.8)	44.1 (12.3)	0.174 ^a
	Median (IQR)	42.0 (31.3–51.8)	47.0 (34.0–52.3)	
Gender, n (%)				
Female		45 (80.4)	67 (77.9)	0.448 ^b
Male		11 (19.6)	19 (22.1)	
Disease stage				
Stage I		44 (78.6)	59 (68.6)	0.425 ^b
Stage II		10 (17.9)	23 (26.7)	
Stage III		2 (3.6)	4 (4.7)	
Extrapulmonary involvement		19 (33.9)	25 (29.1)	0.334 ^b
Duration of follow up (month), median (IQR)		62.5 (32.5–90.8)	60.0 (41.3–120.0)	0.393 ^a
Survival, n (%)				
Died		0 (0.0)	4 (4.7)	0.131 ^b
Survived		56 (100.0)	82 (95.3)	

^aMann-Whitney U test; ^b χ^2 test.

Table 2. Hematological parameters in study groups.

	Remission (n=56)	Chronic course (n=86)	p-value ^a
ACE	53.0 (35.5–82.8)	56.0 (32.8–96.0)	0.666
Neutrophil (10 ⁹ /L)	4.1 (3.2–5.07)	4.3 (3.5–5.4)	0.277
Lymphocyte (10 ⁹ /L)	2.1 (1.6–2.4)	1.7 (1.3–2.3)	0.034
NLR	2.0 (1.6–2.8)	2.6 (2.0–3.1)	0.006
Platelet (10 ⁹ /L)	271.0 (220.3–308.6)	256.3 (216.8–317.0)	0.757
MPV (fL)	8.6 (7.7–9.2)	8.5 (7.9–9.0)	0.784
Platelet/MPV	31.2 (24.3–38.1)	30.6 (25.9–38.4)	0.948
CRP ^b	3.5 (3.0–16.5)	12.5 (4.5–26.5)	0.228

Data are shown as median (IQR). ^aMann-Whitney U test; ^bbased on data from 12 patients in the remission and 10 patients in the chronic groups. ACE: angiotensin-converting enzyme; CRP: C-reactive protein; MPV: mean platelet volume; NLR: neutrophil to lymphocyte ratio. Numbers in bold are statistically significant.

and 10–20% of patients with initial radiological stages I, II, and III, respectively²⁰. Besides, in this study, the ratio of the patients with chronic sarcoidosis was nearly 25%, which was mentioned 10–30% in different studies^{20,21}.

Hematological changes in sarcoidosis include mild anemia, leukocytosis, leukopenia, lymphopenia, eosinophilia, and thrombocytopenia, which were frequently observed in recent studies^{4,22}. Notably, in this study compared with the remission group, the chronic group had a lower lymphocyte count, while a similar neutrophil count was determined during the diagnosis. This seems to indicate the prominent role of lymphocytopenia, as a marker of physiological oxidative stress.

The NLR is a simple composite marker providing the objective measurement of changes in both neutrophils and lymphocytes, while calculated easily from a routine complete blood count without needing extra effort or cost^{4,5,13}. Hence, in this study, the presence of high NLR during diagnosis as a poor prognostic marker seems notable with at least 5-year follow-up.

The NLR is novel prognostic, diagnostic marker for inflammatory diseases^{11,13,14,23}. In the study by İliaz et al., the NLR was found to be supportive in differentiation between tuberculosis and sarcoidosis with the cutoff value of 2.55¹³. In a study by Dirican et al., NLR values were reported to be higher in patients with sarcoidosis than in healthy controls and in extrapulmonary involvement⁵. In a large-scale study by Gungor et al. among patients with sarcoidosis, high NLR (≥ 2.0) values have demonstrated the correlation with well-known inflammatory markers such as ACE, erythrocyte sedimentation rate (ESR), and CRP¹⁴. In this study, since there are limited data about the role of NLR in the chronic sarcoidosis and remission group, the NLR was significantly higher at admission in the chronic sarcoidosis.

Patients with sarcoidosis with stage II and III disease and extrapulmonary involvement were reported to be more likely to have a high NLR⁵. Despite significantly higher NLR in the chronic group in this study, two groups had a similar NLR in terms of initial disease stage and extrapulmonary involvement. Thus, in this study, baseline similarity of disease characteristics between two clinical outcome groups further emphasizes the need for potential biomarkers in sarcoidosis that could predict the disease-specific prognosis following the initial diagnosis.

In recent studies, MPV values were found to be higher in patients with sarcoidosis than in the control group^{5,24}. While the stage increases, no changes in MPV values were detected in the study by Dirican et al.⁵. In contrast, in this study, no significant difference was found between the two groups according to MPV and PLT/MPV values. While serum ACE is the most widely used biomarker of diagnostic and prognostic values in patients with sarcoidosis, it has been associated with relatively low specificity, as elevated serum ACE activity was also shown in multiple granulomatous and non-granulomatous diseases. ACE was also shown to be insignificant in determining the severity of the disease and inappropriate to be used during follow-up⁹. In this study, there was no significant change in serum ACE values measured at the time of admission, between chronic and remission groups.

In recent studies, CRP levels were found to be useful to predict the effectiveness of treatment in chronic pulmonary sarcoidosis. Besides, studies have also analyzed the usefulness of CRP levels reporting higher significant levels with respect to healthy controls²⁵. In this study, according to CRP values, no significant difference was determined between the two groups.

Both stage III sarcoidosis and extrapulmonary involvement were reported to be associated with chronic and progressive diseases and increased the likelihood of relapse²⁰. In this study,

the mortality rate in the chronic group (4.7%) was similar to the meta-analysis designed by Reich et al. (4.8%). The ratio of stage III disease (4.7%) in this study is related to the mortality rate (4.7%).

The major limitation of this study is its retrospective single-center design and relatively low sample size due to the rarity of the disease, which makes our findings not generalizable to the general patient population with sarcoidosis. As patients were asymptomatic in both groups, a measurable outcome in terms of clinical implications of NLR might add strength to the study. Since the data on the prognostic role of inflammatory markers in sarcoidosis are not well defined, our findings make a valuable contribution to the literature.

CONCLUSION

This study demonstrated that the chronic sarcoidosis group had a higher NLR value and lower lymphocyte count at diagnosis compared with the remission group in long-term follow-up. Therefore, NLR values obtained during diagnosis seem to have prognostic value in the long-term monitoring of patients with sarcoidosis in routine clinical practice. The similarity between

chronic and remission groups in terms of initial disease stage and prevalence of extrapulmonary involvement, this study emphasizes the importance of developing novel serum biomarkers to offer a reliable and objective measure to predict disease-specific prognosis among patients with sarcoidosis. Future studies in larger series are needed to justify the diagnostic and prognostic significance of inflammatory markers in patients with sarcoidosis.

AUTHORS' CONTRIBUTIONS

SAB: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **MY:** Conceptualization, Data curation, Writing – original draft, writing – review & editing. **SG:** Conceptualization, Data curation, Writing – original draft, writing – review & editing. **ET:** Investigation, Methodology, Resources, Formal analysis, Writing – original draft, Writing – review & editing. **FTA:** Data curation, Formal analysis, Methodology, Resources, Writing – original draft. **PS:** Conceptualization, Data curation, Resources, Writing – review & editing. **DY:** Data curation, Investigation, Resources, Visualization, Writing – original draft. **SB:** Formal analysis, Investigation, Resources, Writing – review & editing.

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