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Systematic review of the diagnostic role of neutrophil to lymphocyte ratio in sarcoidosis

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Abstract. *Background and aim*: To outline the observations of studies evaluating the prominence of Neutrophil to Lymphocyte Ratio (NLR) in sarcoidosis. *Methods*: The search was performed on PubMed, Scopus, and web of science up until November 21, 2021. Eventually, a number of 17 papers were incorporated into this review. *Results*: The results of this analysis showed no significant difference of NLR values between sarcoidosis patients and tuberculosis patients (SMD=-0.36, 95% CI= -0.92-0.21). The results showed high heterogeneity (I^2=90.83%, p<0.001). So, we used random-effects model. However, NLR can be utilized to identify the radiological severity and staging of pulmonary sarcoidosis due to statistically significant variations. An elevation in NLR values may assist both sarcoidosis diagnosis and lung parenchyma involvement. Also, extra-pulmonary involvement was just more probable to be found in individuals diagnosed with sarcoidosis inhibiting high rates of NLR. High NLR levels were found to be associated with an accelerated rate of progression, revealing that NLR might be used to detect Pulmonary Hypertension (PH) as a complication of sarcoidosis. *Conclusions*: In the visualizations of the disease, NLR was revealed to be a beneficial and straightforward fundamental laboratory biomarker connected to disease severity and requirement for therapy.

Key words: Sarcoidosis; Neutrophil to Lymphocyte Ratio; NLR; Review

Introduction

Sarcoidosis seems to be an idiopathic, multisystem disease with an unclear etiology that is defined by non-caseating granulation tissue which might impact any organ but mainly affects the lungs and mediastinal lymph nodes (1-5). As a multisystem granulomatous disorder, sarcoidosis can affect numerous people all around the world and may appear in people of both genders as well as all age groups and ethnicities (6, 7). Patients are at high threat for pulmonary fibrosis as well as permanent and irreversible organ failure. The illness appears in people who are genetically predisposed to it or who have been exposed to an unidentified pathogen (8, 9). Diagnosis is complicated by the wide range of symptoms, also since many individuals may be asymptomatic, or showing clinical and radiological abnormalities that could be confused with infection or malignancy (10, 11). The clinical manifestations and progression of sarcoidosis seem to be unclear; for instance, it may lead to the formation of a debilitating chronic condition or it may dissolve spontaneously; due to onset it can appear with sensitive nature (including acute Lofgren syndrome), subacute modality or chronic; it can be

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seen in an asymptomatic status or symptomatic and may be accompanied with several comorbidities and challenges (lung fibrosis, renal or cardiac failure, loss of vision or osteoporosis) (12-14).

Granulomatous lung disorders are defined as challenging differential diagnosis for clinicians to make (15, 16). Focal lesions of activated macrophages and lymphocytes within a network of matrix proteins characterize granulomatous inflammation of the lungs. Granulomas are vital defensive mechanisms against mycobacterial and fungal infections, but they can also get extent for non-infectious sources (17, 18). Sarcoidosis is the most common non-infectious cause, with an origin that is not identified completely (19, 20). The term "disease activity" remains ambiguous, but it is frequently misunderstood with the phrase "severity" (21, 22). Many studies involving serological biomarkers, pulmonary and breathing biomarkers, also bronchoalveolar lavage biomarkers to use in diagnosis have been done in recent years. They have, however, been found to have minimal benefits and are not applicable to sarcoidosis (11). The Neutrophil to Lymphocyte Ratio (NLR) is computed by splitting the ultimate number of neutrophils by total count of lymphocytes upon a Complete Blood Count (CBC) (23-26). It has evolved as a biomarker of inflammatory response being used as an indicator in pulmonary and other malignancies, acute coronary syndrome, and prognosis determination in chronically sick patients in the department of intensive care (27-32). It's a cheap, non-invasive, and easy test to perform (33, 34). Although the level of neutrophils rises in inflammatory processes, lymphocyte levels drop. Systemic inflammation may be detected utilizing NLR as a relatively quick and affordable test (35). The impact of NLR in sarcoidosis diagnosis, follow-up, and behavior is unclear, although a few recent types of research suggest that NLR, which measures changes in neutrophils and lymphocytes, could be a viable biomarker for hematological parameters. In this systematic review, we aimed to review the evidences on the role of NLR in the diagnosis, clinical symptoms, treatment, and prognosis of sarcoidosis.

Methods

Sources of data and searching

This research followed the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search strategy was as following ((neutrophil AND lymphocyte AND ratio) OR (neutrophil-to-lymphocyte) OR NLR) AND (sarcoidosis). Scopus, Web of Science, and PubMed was searched up to 13 December 2021. In addition, the reference list of retrieved papers was reviewed manually. The abbreviations used in this study is presented in table 1 and the characteristics of the included studies are shown in table 2.

Selection of studies

The following criteria was used to select the relevant articles: 1) analyzing the prognostic value of NLR in patients with sarcoidosis; 2) reporting NLR obtained from a peripheral blood sample; 3) presenting the diagnostic and prognostic significance of NLR in sarcoidosis. However, case reports, conference papers and editorial letters were not included in this study. All articles obtained through the search were analyzed, and all possibly relevant articles were collected in their entirety. Two independent reviewers separately evaluated entire papers for selection according to inclusion criteria as well as data extraction, besides conflicts resolved by discussion.

Data extraction and quality evaluation

Name of the first author, publication year, number of participants, research methodology (prospective, retrospective), and basic conclusions relevant to sarcoidosis were retrieved from selected studies. The Newcastle-Ottawa Scale (NOS) was applied to determine the quality of studies.

Statistical approach

We pooled the data of numerous studies using the meta-analytic method if there was enough number of publications (≥5). Acquired information was obtained using STATA 14 (STATA Corp., College Station, TX, USA). The primary outcome was the distinction among sarcoidosis patients and TB patients in NLR values. Furthermore, we compared sarcoidosis patients with healthy individuals in NLR values. Standardized mean differences (SMD) with 95 % confidence intervals (CI) was reported. Cochran Q and I^2 statistics were used to determine heterogeneity across studies. A randomized effect model was applied due to significant heterogeneity ($I^2 > 50\%$ or Cochran Q test $p < 0.05$).

Table 1. Abbreviation table.

Abbreviation	Definition	Abbreviation	Definition	Abbreviation	Definition
AUC	Area under curve	IQR	Interquartile range	PRISMA	Preferred reporting items for systematic reviews and meta-analyses
BAL	Blood and bronchoalveolar lavage	LAD	Lymphadenopathy	ROC	Receiver operating characteristics
CBC	Complete blood count	MAIA	Metabolic active inflammatory area	SLR	Systematic literature review
CI	Confidence intervals	NLR	Neutrophil to Lymphocyte Ratio	SMD	Standardized mean difference
COVID-19	Coronavirus disease 2019	NOS	Newcastle-Ottawa Scale	SUVmax	Maximum Standardized Uptake Value
CXR	Chest x-ray	NSAIDs	Nonsteroidal Anti-Inflammatory Drugs	TB	Tuberculosis
DLCO	Diffusing capacity for carbon monoxide	NPV	Negative predictive value	THS	Total HRCT score
ESR	Erythrocyte sedimentation rate	PET/CT	Positron Emission Tomography - Computed Tomography	TLG	Total lesion glycolysis
FDG	Fluorodeoxyglucose	PET/CT SUVmax	Positron Emission Tomography - Computed Tomography Maximum Standardized Uptake Value	WBC	White blood cell
HRCT	High-Resolution Computed Tomography	PH	Pulmonary hypertension	WHO	World Health Organization
ILD	Interstitial lung disease	PPV	Positive predictive value		

Table 2. Characteristics of included studies.

First author	Sample size	Study design	Cut-off point	Year of publication	Country	Outcome
Abedini	88	Retrospective cohort	2.39	2019	Turkey	Serum concentrations of the biomarkers suggested a more vital immunological component in sarcoidosis utilizing NLR.
Balci	150	Retrospective cohort	2.148	2020	Turkey	There was a significant difference among sarcoidosis patients versus control group regarding to NLR values.
Dirican	172	Retrospective cohort	2.0	2016	Turkey	NLR might have a correlation with pulmonary involvement and extra-pulmonary involvement among patients with sarcoidosis.
Iliaz	134	Retrospective cohort	2.55	2014	Turkey	NLR, as a rarely documented marker in pulmonary medicine, was revealed to be beneficial in distinguishing between TB and sarcoidosis.
Karakurt	1039	Retrospective cohort	-	2016	Turkey	There wasn't a significant difference in NLR values between groups having sarcoidosis with ILD.
Kerget	223	Retrospective cohort	2.3	2021	Turkey	The reactive LAP group had considerably higher NLR values.
Kocak	1269	Retrospective cohort	-	2017	Turkey	It was evaluated whether NLR altered with age in the cohort, but no significant difference was detected.

Table 2. (*Continued*)

First author	Sample size	Study design	Cut-off point	Year of publication	Country	Outcome
Korkmaz	167	Retrospective cohort	2.07	2020	Turkey	High NLR values were not correlated with pulmonary hypertension, spontaneous remission, clinical response, or prognosis in any way.
Korkmaz	80	Retrospective cohort	2.07	2020	Turkey	NLR was significantly higher in sarcoidosis patients than healthy controls. In sarcoidosis patients, NLR was significantly higher at stage-2 and -3 than at stage -1 and -4
Ma	2.52	Retrospective cohort	_	2021	Turkey	NLR was not different between sarcoidosis and tuberculous patients.
Mirsaeidi	107	Retrospective cohort	-	2016	Turkey	NLR can be considered as a potential tool in the diagnosis and treatment of PH-induced with sarcoidosis.
Ocal	122	Retrospective cohort	-	2016	Turkey	There were significant variations in mean NLR levels between radiological phases and THS groups.
Onner	41	Retrospective cohort	-	2021	Turkey	A strong correlation between TLG and NLR was detected, as well as a moderately significant correlation between MAIA and NLR. Patients with extra-thoracic involvement also had higher NLR, MAIA, and TLG levels.
Ozdemir	107	Retrospective cohort	-	2021	Turkey	Although NLR is useful to differentiate Stage 1 sarcoidosis from controls but it may not be used to distinguish between Stage 1 sarcoidosis and TB lymphadenopathy.
Rana	105	Retrospective cohort	2.13	2021	Turkey	Peripheral NLR was relatively more prominent in stages 2, 3 and 4 than those in stages 0-1.
Rana	105	Retrospective cohort	2.21	2021	Turkey	The T group had higher NLR level than the NT category.
Tartemiz	80	Retrospective cohort	2.50	2017	Turkey	NLR value in sarcoidosis group was reported significantly higher.
Tartemiz	80	Retrospective cohort	3.20	2017	Turkey	Cases with high NLR values had a significant increased rate of progression.
Yalniz	310	Retrospective cohort	2.40	2019	Turkey	NLR value in group of sarcoidosis was more than the value in the control group. Patients having pulmonary involvement in stages 2–3–4 had significantly higher NLR vs. patients in stage 1.

T: treatment; NT: non-treated

Results

Document screening process and results

During the first assessment, a number of 1066 relevant articles were identified. 185 papers were discarded according to overlap, and 835 studies were eliminated as irrelevant research, as per the inclusion and exclusion criteria. Upon reading full-text articles, 28 studies were eliminated due to a lack of sufficient data, and one research was excluded due to fact that it was a review of the literature. Eventually, 17 studies were reported to be appropriate for this systematic review (Figure 1).

1. NLR in diagnosis of sarcoidosis

1.1. Differentiation of sarcoidosis and its mimics with the role of NLR

1.1.1. Sarcoidosis vs. Interstitial Lung Disease

The NLR ratio has got a lot of interest in recent years as a novel inflammatory measure. Although

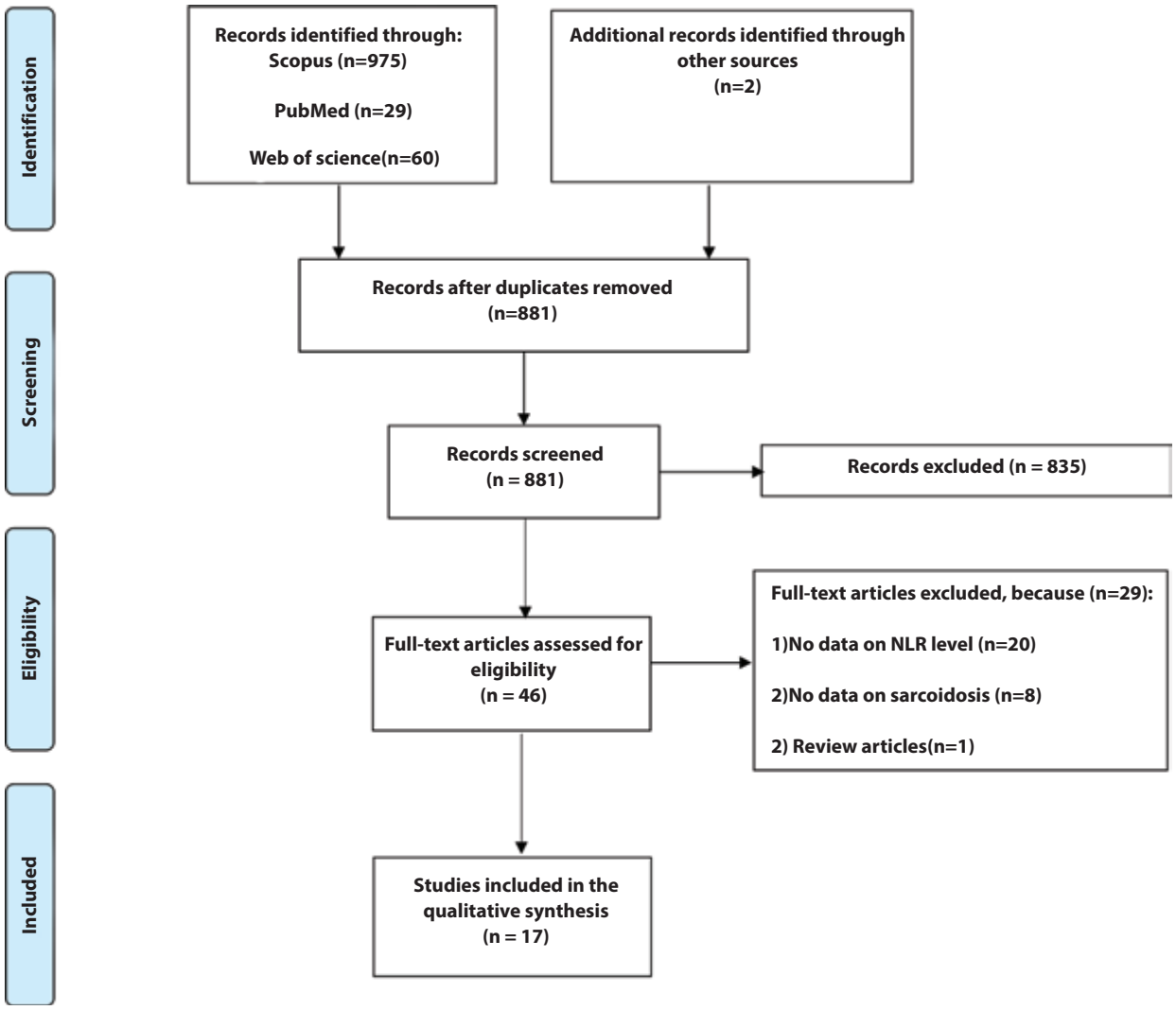


Figure 1. Flow chart of search and study selection.

the association between NLR with lung cancer has been receiving more attention recently, studies on NLR levels in tuberculosis, sarcoidosis, and Interstitial Lung Diseases (ILD) are limited. The relevance of NLR through the differential diagnosis of sarcoidosis and ILD has only been explored in one research.

In a retrospective cohort study conducted by Akturk and colleagues, published in 2017, 1039 individuals were assessed comprising 716 patients diagnosed with sarcoidosis as well as 323 patients with ILD. Data were extracted using the hospital's automation system. In the sarcoidosis group, the NLR was 2.4 (IQR:1.7-3.4), while in the ILD group, it was 2.5 (IQR:1.7-4.4). Furthermore, the difference for NLR value between groups wasn't significant (p=0.53), and the NLR value observed within the sarcoidosis group was pretty low as opposed to the ILD group, but not meaningfully different (36).

Final comment: As a result, it's hard to claim if the NLR values of patients at hospital admission help doctors distinguish between sarcoidosis and ILD, but the outcomes may provide insight for future research. According to the author's opinion, this study had some limitations. It was a retrospective single-center study and the database was built using hospital's automation system, so extensive clinical and radiological evaluations to determine disease activity were not possible. Because both disorders are noninfectious, the NLR values may be identical. Future research

concerning the role of NLR in monitoring patients and differential diagnosis is suggested.

1.1.2. Sarcoidosis vs. Tuberculosis

Five studies compared NLR levels in sarcoidosis patients and Tuberculosis (TB) patients. The pooled results showed that NLR levels were not different between these two groups (SMD=-0.36, 95% CI= -0.92-0.21). The results showed high heterogeneity (I^2=90.83%, p<0.001). So, we used random-effects model.

1.1.3. Sarcoidosis vs Reactive Lymphadenopathy (LAP)

Granulomatous lung disorders are one of the most difficult differential diagnosis for clinicians to make. The role of NLR in distinguishing them has been discussed in a retrospective study by Kerget et al. in which they evaluated the level of NLR comparing sarcoidosis and reactive Lymphadenopathy (LAP). In this observation, 237 patients underwent mediastinoscopy lymph node biopsy, with 83 having sarcoidosis and 65 having reactive LAP. The reactive LAP group had significantly higher NLR values (p=0.012). The Area Under the Curve (AUC) for NLR in patients with granulomatous lymphadenitis and those with reactive LAP was 0.79 (CI: 71–86) in the ROC curve analysis. Also, sensitivity and specificity were 77 % and 80 %, respectively, at cutoff values of 2.3 for NLR (19).

Final comment: In this study, only patients with sarcoidosis stages 1 and 2 were included. The relatively lower sensitivity NLR compared to its specificity in the Receiver Operating Characteristics (ROC) curve analysis was detected. Therefore, Large-scale experiments that encompass all stages of sarcoidosis and investigate parameters with higher sensitivity are needed. Eventually, based on available data, NLR can be a useful biomarker to distinguish between reactive lymphadenitis and granulomatous lymphadenitis.

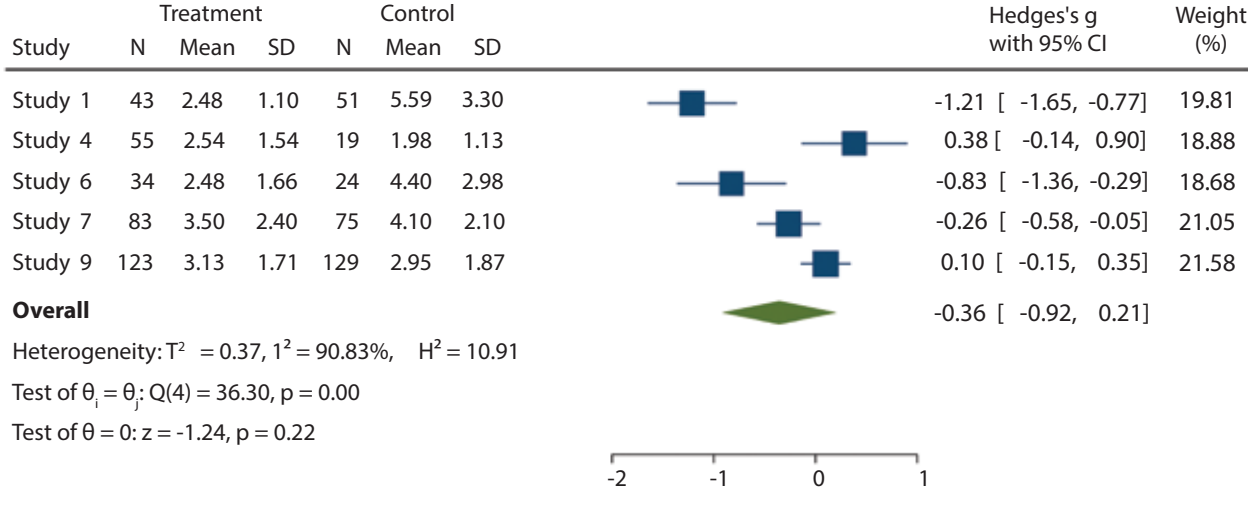
1.2. Role of NLR in sarcoidosis compared with healthy controls

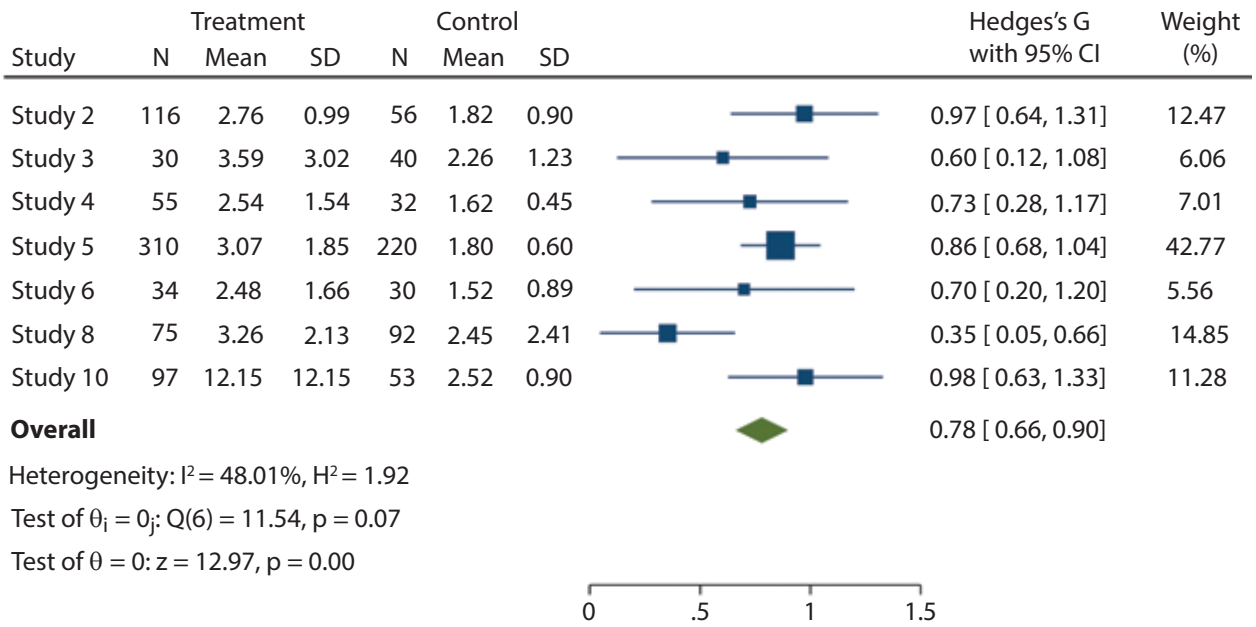
Seven studies compared sarcoidosis patients and healthy controls in NLR levels. The pooled results showed that NLR levels in sarcoidosis patients were higher compared to healthy controls (SMD=0.78, 95%CI= 0.66-0.90). The results showed low heterogeneity (I^2=48.01%, p=0.07). So, we used a fixed-effects model.

2. Relationship between NLR and manifestations of sarcoidosis

2.1. NLR relation with sarcoidosis stage

In about 85-95% of pulmonary sarcoidosis cases, abnormal radiological results are seen. Compared to thoracic computed tomography and other imaging modalities, High-Resolution CT (HRCT) is dominant at evaluating pulmonary parenchymal





abnormalities. The following are the five radiographic stages of pulmonary sarcoidosis: Stage 0: Having normal Chest X-ray (CXR), Stage 1: Only hilarious plus mediastinal lymphadenopathy, Stage 2: Hilarious and mediastinal lymphadenopathy within pulmonary infiltration, Stage 3: Only pulmonary infiltration, Stage 4: Showing pulmonary fibrosis. There is no evidence of pulmonary involvement for stages 0 and 1. Anti-inflammatory medicines, usually corticosteroids, are administered, though treatment varies depending on clinical stage and organ involvement. This staging presents insight into the disease's prognosis.

According to recent clinical trials, NLR, as a marker of alternation revealer in both neutrophils and lymphocytes can be used as biomarker for clinical and laboratory indicators and as a beneficial prognostic agent, particularly for cellular injury caused by inflammation. Whereas a total blood count has been one of the basic sarcoidosis diagnostics, NLR does not require the patient to undergo any further invasive tests. NLR's potential role in the inflammatory process of chronic illnesses has lately been explored. It's a low-cost conceivable marker of inflammation with significant prognostic relevance in inflammatory diseases of the system and cancers. Despite the reality that all imaging modalities have a better success rate, some sarcoidosis cases can be missed while obtaining a definite differential diagnosis of granulomatous lung illnesses. As a result, the identification of sensitive biomarkers is critical for an accurate diagnosis of the condition. We found 8 studies investigating the relevance of NLR with the radiological scope of sarcoidosis.

In a study by Ocal et al. published in 2016, data of 122 patients were evaluated. As the patients' Chest X-rays were examined in terms of conventional radiological stages, 12 (9.83%) of them were categorized as stage 0, 47 (38.52%) as stage 1, 38 (31.15%) as stage 2, 21 (17.21%) as stage 3, and 4 (3.27%) as stage 4. Each patient's total HRCT score (THS) was determined by adding up the total extent score from each radiological lesion. Consequently, every radiological lesion was assigned an overall extent score ranging from 0 to 24. Following that, the THS data were used to divide the patients into four groups. THS=0 points for group 1 (without any parenchymal involvement); 1<THS<20 for group 2 (mild parenchymal extension); 21<THS<30 for group 3 (medium parenchymal extent); THS>31 for group 4 (extreme parenchymal extent). The average NLR scores were 1.28 for stage 0, 1.65 for stage 1, 2.88 for stage 2, 5.47 for stage 3, and 8.48 for stage 4; and in regard of THS divisions, average NLR values were 1.63 in THS group1, 2.01 in THS group2, 3.47 in THS group3, and 5.46 in THS group4; There were significant modifications

in mean NLR levels between radiological phases and THS groups (p<0.001) and significant relevant associations were detected between values of NLR and WBC (r=0.225, p=0.013), NLR and THS (r=0.555, p<0.001), NLR and ESR (r=0.323, p<0.001) (5).

In a study by Yalniz et al. published in 2018, an overall of 310 individuals having sarcoidosis was identified histologically, and 220 normal participants were documented retrospectively. Patients having sarcoidosis were classified into two main categories: those who had stage 0 or 1 of lung parenchymal involvement and others with stages 2, 3 or 4 of radiological extent. It was determined that the NLR value in the group of sarcoidosis was higher than the control group. Patients showing pulmonary involvement in stages 2–3–4 had significantly higher NLR compared with patients in stage 1. Among the 310 participants, 220 of them were in the control group (NLR=1.80.6), 140 were in stage 1 (NLR=2.81.2), 170 were in stage 2, 3, and 4 (NLR=3.32.4). The cut-off value for NLR for identifying the diagnosis was reported as 2.4, respectively. Evaluation of the ROC curve showed an AUC of 0.79 (95% Cl: 76–83), 87% as sensitivity, and 58% as specificity. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for NLR were reported 64% and 85%, respectively (27).

In a study published in 2014, Dirican et al. discovered that as the stage of sarcoidosis rises, so does the ratio of NLR. The main purpose of this research was to discover novel sarcoidosis biomarkers. An overall number of 172 participants were studied in this research, comprising 116 sarcoidosis patients and 56 healthy individuals. Patients having sarcoidosis were classified into two groups based on their stage (stage 0 and 1 vs. stage 2 and 3). In addition, the study group was separated into two categories. The quantity of elevated NLR in patients having sarcoidosis was reported to be larger than those in the control group, as according to NLR [high NLR>2.0) vs. low NLR2.0)]. The outcomes of NLR were significantly different throughout all three groups (p<0.001, respectively). The number of patients with elevated NLR was shown to be more in sarcoidosis patients in comparison to control group, also as the stage progressed, so did the number of participants with high NLR. With the NLR cut-off, evaluation of the ROC curve demonstrated an AUC of 0.83 (CI 68.8–88.4), 80% sensitivity, and 59% specificity. NLR had 80% PPV and 58% NPV, respectively. At the higher stages of disease, there was a positive and statistically significant correlation across increased sedimentation and NLR (r=0.183, p=0.017) (4).

In a study by Korkmaz et al. published in 2020, 75 patients with sarcoidosis, and 92 participants as a control group with close demographic information were included. By comparing NLR values regarding to stage, no major variations were identified between stage 1, 2, 3, and 4 of sarcoidosis patients (3.26 ± 2.13). However, the NLR ratio was significantly higher than the control group (2.45 ± 2.41) (p<0.001). Since the association between NLR and C-reactive protein (CRP) was studied, it was observed that there was a little favorable correlation (r=0.31, p=0.06) without any positive correlation between NLR and ESR (p=0.11). Regarding the relation between NLR among blood CD4/CD8 and blood and bronchoalveolar lavage (BAL) CD4/CD8 ratios, a substantial positive correlation among NLR and blood CD4/CD8 was observed (r=0.558, p=0.02). A significant positive association was identified between NLR and BAL CD4/CD8 ratio (r=0.65, p=0.01). In patients having sarcoidosis, mean NLR ± SD (n=75) was 3.26±2.13 while in controls, mean NLR ± SD (n=92) was 2.45±2.41 (p-value<0.001). Also, Stage 1 and 4, mean NLR ± SD (n=23) was 2.23±0.85 and Stage 2 and 3, mean NLR ± SD (n=52) was 3.72±2.36 (p-value=0.003). However, it is important to note that there was only ONE patient with stage 4 sarcoidosis within the analysis of Stage1+4 vs. Stage 2+3. The ROC curve was drawn for the sensitivity and specificity of NLR. The cut-off point was determined as 2.07, and the sensitivity and specificity ratios were reported as 68% and 61%, respectively. The PPV and NPV of the NLR group were reported as 58% and 70%, respectively (8).

In a retrospective study published by Kerget et al. in 2020, 223 patients were included in the study; 83 had sarcoidosis, 75 had TB, and 65 had reactive LAP. NLR samples were assessed as follows: TB group=4.1±2.1, LAP group=2.4±2.1, and sarcoidosis group=3.5±2.4. NLR values in the TB and sarcoidosis groups were not statistically different (p-value=0.3) but were significantly higher than those of the reactive LAP group (p=0.001, p=0.012). In this study, 40 patients with sarcoidosis were classified as stage 1 with an NLR value of 2.8±2.2 and 43 as stage2 with an NLR value of 4.2±2.4 (p=0.01). In

ROC curve analysis of NLR in patients developing granulomatous lymphadenitis and patients having reactive LAP, the AUC was 0.79, respectively (CI: 80–91, CI: 71–86). At cutoff values of 2.3 for NLR, sensitivity was 77%, and specificity was 80%, respectively. ESR of both groups was substantially associated with NLR value (r=0.499, p=0.001) (19).

In a study by Rana et al. 105 patients (IQR median age, 56 (47-63)) were incorporated retrospectively in the research. Chest X-ray score was conducted and patients who were reported to be in stages 0 and 1 of CXR were classified together, but so were those in stages 2, 3 and 4; the other adjusted parenchymal invasion. Peripheral NLR was quite higher in stages 2, 3 and 4 than those in stages 0-1 (median IQR, 1.98 (1.45-3.13) vs. 2.6 (1.89-3.86), p=0.0090). NLR ratio for each stage was calculated as stage 0 = 1.904 (1.4-2.7), stage 1 = 2.549 (1.8-3.9), stage 2 = 2.504 (1.8-3.9), stage 3 = 2.444 (1.7-3.2), stage 4 = 2.807 (1.6-3.5). (1.6-3.5). Evaluation of ROC curve categorized these two groups as per NLR with an AUC of 64% (95% CI 54-74) and a maximum cut-off point of 2.13 (54.3% specificity,70.4% sensitivity) (12).

In a retrospectively observed cohort study by Kocak et al. published in September 2017, a total of 1269 patients with a diagnosis of sarcoidosis were contained and divided into the following groups: first group: pulmonary sarcoidosis, in which the diagnosis is defined by histopathological shreds of evidence and lung parenchyma involvement; Second group: Lymph node sarcoidosis; in which the diagnosis is determined by histological features and mediastinal lymphovascular invasion; and third group: Pulmonary sarcoidosis combined with lymph node sarcoidosis; in which histological features as well as pulmonary parenchymal and mediastinal lymph node involvement are utilized to make diagnosis. Groups were evaluated as per laboratory parameters and, NLR was not varied across groups (first group= 3.3±2.5, second group=2.9±2.0 and third group=3.2±2.4; p-value=0.41) (6).

Tartemiz et al. enrolled 40 sarcoidosis patients and 40 healthy control participants in their study. As sarcoidosis patients in stages 2, 3, and 4 were compared to those in stage 1, the average NLR levels were significantly higher (respectively 4.82±4.05, 2.59±1.12, p=0.018) (1).

Final comment: As a conclusion of the summarized studies, NLR may be utilized to identify the radiological severity of pulmonary sarcoidosis due to mostly statistically meaningful variations in average NLR values across radiological stages. Also, elevation in NLR values may assist both sarcoidosis diagnosis and lung parenchymal involvement. In the visualizations of the disease, NLR was revealed to be a beneficial and straightforward fundamental laboratory biomarker connected to disease severity and requirement for therapy. Future studies are needed to determine a suitable cut-off value to be potentially used to differ between stages 0-1 vs. stages 2-3-4.

2.2. NLR and thoracic involvement

Sarcoidosis can be subclinical or detectable by unintentionally obtained chest radiography. Symptoms are typically related to an afflicted organ or the proportion of the system's activity. Quite often, affected organs are the pulmonary and thoracic lymph nodes. Extra-thoracic involvement occurs in 25 to 50% of cases and is often associated with thoracic involvement. We found 2 studies defining the relevance of NLR with thoracic involvement in patients diagnosed with sarcoidosis.

In a study by Tartemiz et al. 40 sarcoidosis and 40 regular control patients were enrolled. Considering the individuals of both groups; the NLR value in the sarcoidosis group was reported dramatically higher (3.59±3.02 for sarcoidosis and 2.26±1.23 for the control group; p-value=0.012, respectively). The mean NLR levels in sarcoidosis patients in stages 2, 3, and 4 were significantly higher than those in stage 1 (respectively 4.82±4.05, 2.59±1.12, p=0.018). When the NRL cut-off point for sarcoidosis was kept at 2.50, the AUC was calculated to be 0.71 (CI 60.2-83.0), sensitivity was 70.0%, and specificity was 65.0%. The detected involvement of mediastinal lymph node was in 38 (95%) individuals, and the pulmonary parenchymal invasion was found in 22 (55%) participants in the Positron Emission Tomography - Computed Tomography (PET/CT). By far, PET/CT revealed pulmonary parenchymal involvement in 22% of cases who did not demonstrate parenchymal invasion by HRCT. In contrast, no involvement in PET/CT was related to lung parenchymal abnormalities of HRCT in 38.7% of patients (p=0.039). Among patients with or without parenchymal involvement in PET/CT, no differences were detected regarding NLR and clinical

manifestations (p>0.05). Forecasting the evolution, for Positron Emission Tomography - Computed Tomography Maximum Standardized Uptake Value (PET/CT SUVmax) cut-off point was 9.5, for NLR cut-off level 3.20, the AUC was calculated to be 0.79 (CI 62.2-96.5), sensitivity was 80.0% and specificity was 76.7% (1).

In another research conducted by Onner et al., conducted at 2020, 41 patients were enrolled. They presented a range of symptoms, such as cough in 24 (58.54%), fatigue in 19 (46.34%), and shortness of breath in 15 (36.59%). NLR was confirmed to have a mean value of 3.34. As the correlation between PET/CT data and NLR was analyzed, a strong correlation between Total Lesion Glycolysis (TLG) and NLR was detected, as well as a moderately significant correlation between Metabolic Active Inflammatory Area (MAIA) and NLR (r-values=0.852, 0.660, respectively; p-value for both correlations<0.001). All of the patients had thoracic involvement, and they were categorized into two groups: those who only had thoracic involvement [24 (58.54 %)] and those who had extra-thoracic involvement besides [17 (41.46 %)]. In terms of MAIA, TLG, and NLR values, there was a significant difference beyond these two groups (p values: 0.002, 0.001 and 0.003, respectively). Even though the patients were categorized depending on their manifestations, no significant differences in Maximum Standardized Uptake Value (SUVmax), MAIA, TLG, or NLR values were detected. Also, as the patients were classified based on revealing symptoms, no significant differences in SUVmax, MAIA, TLG, or NLR values were revealed (37).

Final comment: According to the mentioned studies, NLR value in patients with sarcoidosis was significantly higher than healthy controls. However, there was no significant association between NLR and clinical manifestations of sarcoidosis.

2.3. NLR and extra-thoracic involvement

Considered a chronic disease with granulomatous base, sarcoidosis may impact many people throughout the world. In addition to appraisal of symptoms such as pulmonary infiltration, bilateral hilar lymphadenopathy, ophthalmic and dermal lesions, it can also impact the hepatic system, cardiac system, spleen, brain (CNS), salivary glands, heart, muscles, bones, as well as other organs. We found two studies describing the role of NLR with extra-thoracic involvement in patients diagnosed with sarcoidosis.

In an investigation performed by Korkmaz et al. 56 individuals with sarcoidosis showed only pulmonary involvement, whereas 29 manifested both pulmonary and extra-pulmonary involvement. The impacted sites of extra-pulmonary clinical features were as follows: nine dermal involvements, seven cardiac involvements, four showed symptoms of Leöfgren's syndrome, three extra-thoracic lymph node involvements, two eyes, one parotid gland involvement, one kidney involvement, one neurologic involvement, and one rectum involvement. In terms of NLR, there was no significant difference between patients having pulmonary involvement exclusively or those with extra-pulmonary involvement combined with pulmonary involvement, as well as between the categories among those with extra-pulmonary involvement (p=0.46) (8).

In a study released in 2014, Dirican et al. an aggregate total of 172 people was chosen for this research, consisting 116 sarcoidosis patients and 56 healthy participants. The clinical features like shortness of breath, coughing, exhaustion and chills were more frequently detected in radiologically highly developed patients. However, there wasn't any difference in other complaints. Once the association across high-NLR and low-NLR individuals and clinical signs was studied, symptoms related to pulmonary dysfunction, such as coughing and breathing difficulties, were observed more often in patients with high-NLR (p=0.008 and p=0.032, respectively). The latter symptoms were also detected more frequently in individuals showing high NLR, however, this did not approach statistical significance. Despite the prevalent observation of extra-pulmonary involvement in high NLR individuals, this difference illustrated relevance, particularly in patients with the cutaneous involvement (p=0.032) (4).

Final comment: A significant limitation of the described studies is their retrospective origin. However, it can be concluded that extra-pulmonary involvement, particularly cutaneous involvement, is just more probable to be found in patients having sarcoidosis with high rates of NLR. Furthermore, symptoms like coughing and shortness of breath are reported more often in high NLR

patients. This scenario may be accompanied by diffuse lung involvement. But considering the limits, these clinical observations reveal that the NLR may have association with extra-pulmonary involvement along with pulmonary involvement in sarcoidosis.

3. NLR and prognosis of sarcoidosis

3.1. NLR and response to treatment

It has been shown that NLR value is compromised in multiple clinical situations, including cancers, morbidities of lungs and heart and several inflammations. Also elevated rates are associated with increased morbidity, but decreased levels are correlated with better prognosis, and might be considered as components of acute inflammation. For example, chemotherapy effectiveness has been discovered to behave stronger in participants with decreased NLR in lung cancer, but participants with decreased NLR are correlated with better prognosis. We found 3 studies that specify the impact of NLR in the therapeutic response of sarcoidosis.

In a study by Yalniz et al. data from 310 patients diagnosed with sarcoidosis and 220 normal controls participants were reviewed retrospectively. Patients with sarcoidosis had substantially larger NLR than the control group, and patients having pulmonary involvement in stages 2–3–4 had significantly higher NLR vs. patients in stage 1. An overall number of 83 (26.7%) patients were administered with medicine containing steroids and/or methotrexate medication, and a majority of 72 patients out of 83 completed the treatment. NLR value before treatment was 3.38±3, after treatment was recorded 2.93±1.7 (p-value=0.258) (27).

In a study by Korkmaz et al. including 75 sarcoidosis cases and 92 individuals, spontaneous recovery was reported in 27 (36%) patients during the study, but not in the other 48 (64%). Furthermore, there was no significant difference in NLR values across both the categories with and without complete recovery (p=0.15). 33 people (44%) were chosen not to receive any medical treatment. 27 of the 33 untreated patients proceeded into spontaneous remission but six patients did not get to complete remission would just be medicated as per follow-up if recurrence presented. Despite this, 42 (56%) of our patients were on a treatment regimen that included methylprednisolone, methotrexate, infliximab, local steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs). There wasn't any meaningful difference in NLR between patients receiving treatment and those who did not (p=0.12) (8).

In a study by Rana et al. 105 patients (IQR median age, 56 (47-63)) were included retrospectively. These patients were split into two groups depending on their medication status: Treated (T) versus Non-Treated (NT). 73 patients (57%) were on pharmaceutical treatment (T group) at the time of the study, containing prednisone (n=40, 53%) plus Disease-Modifying Anti-Rheumatic Drugs (DMARDs, such as methotrexate, azathioprine, hydroxychloroquine) (n=33, 43%). Among the T group, a number of 47 patients (74%) had been on consistent sarcoidosis medication for an optimum of 12 months, whereas 26 (36%) received only a renewed prescription. At the time of admission, 56 patients (43%) were not obtaining any therapy (NT group). 15 of them (27%) quit medication treatment during the past 12 months owing to symptomatic, functional, and/or radiological remission. In contrast, the residual 41 (73%) demonstrated full disease remission and did not need therapy in the preceding 12 months. 42 patients (57%) who underwent treatment at the time of the previous examination were symptomatic, with the most frequent symptoms including persistent dry coughs, exhaustion, and muscle and joint pain. The T group had a more prominent NLR level than the NT category (mean IQR, 2.79 (1.78-3.84) versus 1.98 (1.51-2.67), p=0.0034). Considering an AUC of 65.3 % (% CI 55.6-74.9) and an optimum cut-off point of 2.21, evaluation of ROC analysis classified these two groups based on NLR value (specificity of 74% and sensitivity of 61%) (12).

Final comment: It is revealed that sometimes there might be a decline in NLR values in patients who benefit from treatment approach and receive the improved status of health, and NLR is demonstrated as a practical and straightforward essential laboratory marker associated with illness development and the requirement for therapy in the diverse settings of this status. Anyway, further investigation can strengthen the validity of this hypothesis.

3.2. NLR and development of pulmonary hypertension

Pulmonary Hypertension (PH) is a critical consequence in sarcoidosis. It is a significant negative prognostic factor, which explains why these patients

are given higher urgency in orthotopic pulmonary transplantation. PH is indeed a vasculopathy that results from increased vascular cell proliferation, while inflammation plays a pivotal role. The impact of NLR in development of PH has only been explored in one research.

In a retrospective study conducted by Mirsaeidi et al. an overall of 107 people who had sarcoidosis were enrolled in the research, among whom 28 patients (26%) showed signs of PH and the duration of sarcoidosis was 12 years. Transthoracic echocardiography (TE) was used to evaluate the presence or absence of PH whenever the systolic pressure of the pulmonary artery was more than 25 mmHg. Patients with PH were much older than individuals with sarcoidosis who did not have PH (57.1±8.8 vs. 51.9±9.3 years, p=0.011). Multiple regression techniques with backward reduction were utilized to see if NLR was individually incorporated with PH among sarcoidosis patients. Patients with PH who had sarcoidosis had a high NLR (4.1±2.9 vs. 3.2±2.4, P=0.120). In patients with sarcoidosis having PH, NLR>3.5 developed with a significant higher frequency (50% vs. 24%, p=0.016). The sensitivity as 50 %, specificity as 78 %, PPV as 41.9 %, and as of 81.4 % with an AUC of 0.619 was established being the most relevant cutoff point for NLR for distinguishing sarcoidosis patients with or without PH. NLR>3.5 remained substantially connected with PH in its multiple regression model (OR 3.254, 95 percent CI 1.094–9.678, P=0.034). In this retrospective study, an independent association was revealed between NLR, a measure of inflammatory response, and PH among sarcoidosis patients. Nonetheless, as predicted, a higher NLR (>3.5) in sarcoidosis suggests a more vigorous inflammatory reaction, which could be the primary component and pathophysiological basis for the formation of PH (38).

Final comment: As a conclusion of this research, NLR can be considered as a potential tool in the diagnosis and treatment of PH-induced with sarcoidosis. It can be notices as a suitable negative test due to the reasonable specificity (78%) with NPV (81.4). Therefore, the significant NPV makes it an impressive strategy for excluding PH in patients diagnosed with sarcoidosis. Additional studies are necessary to investigate the utility of NLR for detecting sarcoidosis-affiliated PH and verify outcomes prior to getting utilized in the primary healthcare context.

3.3. NLR and disease progression in sarcoidosis

Sarcoidosis has an excellent prognosis. In two-thirds of patients, spontaneous remission occurs, whereas the remaining becomes chronic. In 10-15% of cases, slow development is seen, with lung fibrosis emerging as a result. Pulmonary fibrosis, along with cardiac and neurological dysfunction, are the most common causes of mortality. Furthermore, the severity of the illness has little impact on the progression, clinical prognosis, or therapy response. Two studies aimed to clarify the impact of NLR in progression of sarcoidosis.

Tartemiz et al. enrolled 40 sarcoidosis patients and 40 healthy control participants in their study. When the status of patients' progression was examined at the end of a year, it was discovered that cases with high NLR and PET/CT LAP SUVmax values with lower diffusing capacity for carbon monoxide (DLCO)% values had a statistically significant high score of progression (p<0.05). For estimating progression, the AUC for the NLR cut-off point 3.20 was 0.79 (CI 62.2-96.5), sensitivity seemed to be 80.0 %, specificity 76.7 %, and the AUC for the PET/CT SUVmax cut-off point 9.5 was 0.71 (CI 46.6-95.9), sensitivity 70.0 % and specificity 82.1% (1).

In a study by Korkmaz et al. the study group consisted of 75 sarcoidosis patients and 92 people as control group. According to the patients' most recent evaluations, 48 (64%) of them had relapses, 24 participants (32%) had stability, and 3 of them (4%) had progression. There wasn't any notable change between these groups regarding to NLR (8).

Final comment: Prognosis of sarcoidosis in most cases is quite good and the most prevalent cause of mortality is lung fibrosis. But it seems like there isn't enough evidence stating the role of NLR in the progression of disease.

4. NLR and related factors

Sarcoidosis mainly attacks the respiratory and lymphatic organs and can develop in people of various ages, races, and ethnicities. Nevertheless, the highest incidence seems to be in individuals between 20 and 39 years old. We included three studies in this topic.

In a retrospective study by Kocak et al. a total of 1269 patients were evaluated. According to their age, individuals were categorized into three groups.

Patients in groups 1, 2, and 3 ranged in age from 20 to 39, 40 to 59, and 60 to 80 years old, correspondingly. The laboratory variables were used to assess the groups. Data demonstrated that elderly individuals with sarcoidosis (>60 years) were more probable to be female, and the NLR was not varied across groups (p=0.41) (39).

In a study by Akturk et al. 1039 individuals were included and categorized in two subgroups of sarcoidosis and control group. The median age of the sarcoidosis subgroup was 49 ± 14 years, whereas the mean age of the ILD patients was 60 ± 17 years. Mean NLR level in sarcoidosis subgroup was (IQR median age 2.4 (1.7-3.4)) and in the control group (IQR median age 2.5(1.7-4.4)) (p-value>0.005). There was a meaningful disparity in median age distribution among two categories.

In the research conducted by Onner et al. 41 patients diagnosed with sarcoidosis were included wherein 11 (26.83%) patients were male and 30 were female (73.17%). Sixteen of the patients (39.02%) were current smokers or had smoked previously. In the categorization established related to gender, no considerable difference was identified with both PET/CT parameters and NLR value (37).

Final comment: Sarcoidosis can be seen in people all around the world without any differences in terms of age. As indicated in the studies above, there wasn't any significant difference in NLR value between groups of younger or senior individuals.

5. Conclusions

In this study, we have presented a comprehensive overview of the literature on the association of NLR with sarcoidosis, known as an illness with variable clinical characteristics (40). Pulmonary sarcoidosis is accompanied by an unexpected pattern, with some individuals exhibiting spontaneous remission while others proceed to chronic lung disease causing lung fibrosis or PH (41). Equal annual follow-up is indicated for clinical and subclinical sarcoidosis patients at initial stages (12). NLR, as a novel biomarker of inflammation, is shown to be a significant prognostic predictor in malignancies and inflammatory illnesses, ranging sarcoidosis, and can be easily be assessed from a typical CBC derived by splitting the total neutrophil count by the number of lymphocytes (4, 6, 28). It is a quick, repeatable, and cost-effective test, also fast and responsive as a prognostic factor that outperforms other hematologic markers in predicting the prognosis of sarcoidosis patients (4). As a result, NLR can be used as an easy and cheap measurable marker to demonstrate inflammation in sarcoidosis. Studies demonstrating the association of NLR with staging and activity will extend the use of this biomarker in clinical practice (42). We think that the data in our study will shed light on future studies concerning data and methods. Consequently, we propose that the elevation in NLR levels can be a clue for both diagnosis, detection of disease severity and involvement of pulmonary parenchyma and that our results could be verified by prospective studies covering larger populations to clarify the relevance through these variables in prognosis (8, 19). Large-scale studies that incorporate all stages of sarcoidosis and research measures with higher sensitivity are recommended.

Data Availability: All data generated or analysed during this study are included in this published article.

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