The utility of neutrophil-to-lymphocyte ratio determined at initial diagnosis in predicting disease stage and discriminating between active and stable disease in patients with sarcoidosis: a cross-sectional study

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Abstract

Objective: To evaluate the utility of neutrophil–lymphocyte ratio (NLR) determined at initial diagnosis in predicting advanced disease stage and discriminating between active and stable disease in sarcoidosis.

Methods: A total of 465 patients with biopsy-proven sarcoidosis (age: 47 years, 70.5% females) were included in this retrospective cross-sectional study. Data on patient demographics, sarcoidosis stage, clinical status (stable and active), anti-inflammatory treatments, complete blood count, and inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet/mean platelet volume (MPV) ratio were recorded. NLR values were compared by subgrouping the patients according to the stage of sarcoidosis and clinical status, while the receiver operating characteristics (ROC) curve was plotted to determine the role of NLR in the identification of disease activity with the calculation of area under the curve (AUC) and cutoff value via ROC analysis.

Results: Overall, active, and stable disease was evident in 36 (7.8%) and 427 (92.2%) patients, respectively. Median NLR values were significantly higher in patients with active disease compared with stable disease (3.31 (2.34–4.31) vs. 2.29 (1.67–3.23); p = 0.005). Advanced sarcoidosis stage was associated with significantly higher NLR values at stages 0, I, II, III and IV, respectively (p = 0.001). ROC analysis revealed an NLR cutoff value of ≥2.39 (AUC 95% CI): 0.70 (0.62–0.79), p < 0.001) to discriminate between active and stable disease with a sensitivity of 72.0% and specificity of 52.0%. The significantly higher percentage of patients with active vs. stable disease had NLR values ≥2.39 (74.0% vs. 47.0%; p = 0.002).

Conclusion: Our findings indicate the potential utility of on-admission NLR values to predict the risk of advanced disease stage and to discriminate between active and stable disease in sarcoidosis. Measured via a simple, readily available, and low-cost test, NLR seems to be a valuable marker for monitoring disease activity and progression.

Introduction

Sarcoidosis, an inflammatory granulomatous disease of unknown etiology, is characterized by pulmonary involvement in most cases along with a variable clinical course and unpredictable natural history and prognosis [1–3]. Although progression to fibrosis and risk of permanent organ impairment is evident in one-third of patients [4,5], sarcoidosis has no specific treatment modality or pathognomonic markers of clinical outcome due to its unknown etiology [1,5–8]. Hence, the identification of potential markers for disease activity and progression is considered critical for better management of these patients [1,5,6,9,10].

Neutrophil–lymphocyte ratio (NLR) has been recently emerged as a cost-effective and practical inflammatory marker with the diagnostic and prognostic value shown in several respiratory and cardiac diseases [11–15]. In accordance with consideration of sarcoidosis as a systemic inflammatory disease with the formation of granulomas in the affected organs [1,5,11], the increase of NLR in sarcoidosis compared with the control group has also been demonstrated by several studies [7,10,16,17].

However, while a need for objective disease-specific biomarkers that can predict clinical course, severity, and prognosis of sarcoidosis has long been recognized [4,7,9], the relation of NLR with severity or progression of sarcoidosis remains unknown since limited data are available on the role of NLR in the monitoring of sarcoidosis patients [6,7,10,11,16,18–20].

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This retrospective study was therefore designed to evaluate the utility of NLR determined at initial diagnosis in predicting advanced disease stage and discriminating between active and stable disease in patients with biopsy-proven sarcoidosis.

**Methods**

**Study design and population**

This retrospective cross-sectional study was conducted at a tertiary care sarcoidosis out-patient clinic, serving for follow-up of the sarcoidosis patients by pulmonologists particularly interested in interstitial lung diseases. Of 1198 prevalent sarcoidosis (ICD-10-D86 and subcodes) patients followed up between January 2016 and July 2017, 465 patients with biopsy-proven sarcoidosis (mean (SD) age: 47.0 (12.0) years, 70.5% were females) were included in this study. Age over 18 years, presence of histopathological diagnosis, and complete blood count findings on initial diagnosis were the inclusion criteria of the study. Patients with co-morbid silicosis, tuberculosis, malignancy, or rheumatologic disease were excluded from the study.

The study was conducted in full accordance with local GCP guidelines and current legislation, while the permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Flow chart of the study Figure 1.

**Variables**

Data on patient demographics (age, gender), sarcoidosis stage (0-IV), clinical status (stable disease and active disease), anti-inflammatory treatments, complete blood count (CBC), and inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet/mean platelet volume (MPV) ratio at the time of initial diagnosis were retrieved from hospital information system (HIS). NLR values were compared by subgrouping the patients according to the stage of sarcoidosis and clinical status, while receiver operating characteristics (ROC) curve was plotted to determine the role of NLR in the identification of disease activity with the calculation of area under the curve (AUC) and cutoff value via ROC analysis.

Active disease was considered for patients with an increase in dyspnea from clinical complaints on admission, and patients with radiological progression. Stable disease was defined as the absence of any of the findings explained above, regardless of whether the patient received treatment.

**Hematological analysis**

CBC analysis was performed via the method of flow cytometry (Beckman Coulter LH 780 Analyzer; Beckman Coulter Inc., Miami, FL, USA). Serum CRP levels were determined by the turbidimetric method (Toshiba ACCUTE TBA-40FR; Toshiba Medical Systems, Tokyo, Japan). NLR was calculated as the ratio of neutrophil to lymphocyte counts, and the ratio of the platelet count to MPV was also calculated.

**Statistical analysis**

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Fisher’s
exact test and Pearson chi-square analysis were performed for categorical variables. Mann–Whitney U-test was used to analyze non-normally distributed numerical data, while Student t-test was used for normally distributed data. ROC curve was plotted to determine the role of NLR in the identification of disease activity with the calculation of AUC and cutoff value via ROC analysis according to the maximal Youden index. 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

Demographic characteristics and disease activity

The mean patient age was 47.0 (SD 12.0) years, and 328 (70.5%) patients were female patients. Overall, active and stable disease was evident in 36 (7.8%) and 427 (92.2%) patients, respectively.

CBC findings and inflammatory markers according to disease activity

Active vs. stable disease was associated with significantly higher leukocyte (median (min-max) 8.16 (6.70–11.6) vs. 6.70 (5.80–8.00) 10^9/L, p = 0.005), neutrophil (5.25 (4.30–8.85) vs. 4.00 (3.30–5.00) 10^9/L, p = 0.001) and monocyte (0.63 (0.50–0.90) vs. 0.53 (0.43–0.70)%, p = 0.016) counts, RBC levels (4.98 (4.80–5.50) vs. 4.85 (4.52–5.18) 10^12/L, p = 0.005) and RDW (14.70 (13.70–16.05) vs. 14.07 (13.40–15.00), p = 0.035), whereas with lower eosinophil counts (1.56 (0.45–2.89) vs. 2.39 (1.50–3.80)%, p = 0.008) (Table 1).

Median (min-max) NLR values were significantly higher in patients with active disease compared to those with stable disease (3.31 (2.34–4.31) vs. 2.29 (1.67–3.23), p = 0.005) (Table 1).

ROC analysis

ROC analysis revealed a NLR cutoff value of ≥2.39 (AUC (95% CI): 0.70 (0.62–0.79), p < 0.001) to discriminate between active and stable clinical status with a sensitivity of 72.0% and specificity of 52.0% (Figure 2).

Significantly higher percentage of patients with active vs. stable disease had NLR values ≥2.39 (74.0 vs. 47.0%, p = 0.002) (Table 3).

Discussion

Our findings revealed the association of higher NLR values detected on initial diagnosis with a more advanced disease stage and an active clinical status in patients with biopsy-proven sarcoidosis, while a NLR cutoff value of ≥2.39 (72.0% sensitivity and 52.0% specificity) was determined to discriminate between active and stable disease.

Although elevated NLR is an expected and previously demonstrated finding in patients with a systemic inflammatory disease such as sarcoidosis when compared to control subjects [7,10,16,17], our findings indicate the likelihood of further elevation of NLR (≥2.39) to correlate with advanced stage and active clinical state in sarcoidosis patients.

Likewise, in a past study among sarcoidosis patients, NLR values were reported to be significantly higher in those with parenchymal involvement (stage 2,3,4) compared to those without parenchymal involvement (stage 0,1), while a NLR cutoff value of 2.4 (87% sensitivity and 58% specificity) was shown to discriminate between advanced and milder disease stage [17]. In addition, in the past a study with 116 sarcoidosis patients and 56 healthy individuals, a NLR cutoff value of ≥2 (80% sensitivity and 59% specificity) was reported to discriminate between sarcoidosis patients and healthy controls, along with an increased likelihood of higher NLR values in patients with extrapulmonary involvement [10].

In a past study with 122 sarcoidosis patients, NLR was reported to significantly differ with respect to radiological stages (mean 1.28 in stage 0 and 8.48 in stage 4) and parenchymal involvement (mean 1.63 and 5.46 in total HRCT score group 1 and group 4, respectively) [7]. The authors also noted the association of NLR with more severe parenchymal involvement and thus its potential role to predict the radiological extent of pulmonary sarcoidosis [7]. In a past study with 40 sarcoidosis patients, NLR values in sarcoidosis cases of stages 2,3, and 4 were reported to be significantly

**CBC findings and inflammatory markers according to the stage of sarcoidosis**

Advanced sarcoidosis stage was associated with significant increase in serum leukocyte (p = 0.024), neutrophil (p = 0.005), monocyte (p = 0.002), CRP (p = 0.026) levels (Table 2).

Advanced disease stage was also associated with significantly higher NLR values (median (min-max) 1.95 (1.58–2.59), 2.27 (1.65–3.26), 2.56 (1.84–3.73), 2.29 (1.83–3.81) and 4.83 (2.94–6.71) at stages 0, I, II, III and IV, respectively, p = 0.001) (Table 2).

| Table 1. Complete blood count and inflammatory markers according to disease activity. |
|---|---|---|---|---|---|
| Clinical status | Median (min-max) | Active disease (n = 36) | Stable disease (n = 427) | p value |
| Leukocyte, 10^9/L | 8.16 (6.70–11.6) | 6.70 (5.80–8.00) | 0.005 |
| RBC, 10^9/L | 4.98 (4.00–5.50) | 4.85 (4.52–5.18) | 0.005 |
| Hemoglobin, g/dL | 13.70 (12.45–14.55) | 13.40 (12.30–14.69) | 0.61 |
| Hematocrit, % | 41.3 (37.8–42.8) | 39.8 (37.0–43.2) | 0.08 |
| MCV fl | 82.5 (76.9–84.2) | 83.0 (79.3–85.3) | 0.39 |
| RDW | 14.70 (13.70–16.05) | 14.07 (13.40–15.00) | 0.035 |
| Neutrophil, 10^9/L | 5.25 (4.30–8.85) | 4.00 (3.30–5.00) | 0.001 |
| Monocyte, % | 0.63 (0.50–0.90) | 0.53 (0.43–0.70) | 0.016 |
| Lymphocyte, 10^9/L | 1.73 (1.25–2.35) | 1.80 (1.40–2.20) | 0.67 |
| Eosinophil, % | 1.56 (0.45–2.89) | 2.39 (1.50–3.80) | 0.008 |
| MPV | 8.3 (7.4–9.0) | 8.4 (7.8–9.0) | 0.87 |
| Platelet, 10^9/L | 273 (237–328) | 262 (221–310) | 0.17 |
| NLR | 3.31 (2.34–4.31) | 2.29 (1.67–3.23) | 0.005 |
| Platelet/MPV | 32.32 (28.25–42.85) | 31.62 (25.05–38.50) | 1.00 |
| CRP, mg/dL | 6.0 (3.3–14.2) | 5.5 (3.3–10.4) | 1.00 |
| ESR, mm/h | 30 (12–41) | 31 (19–47) | 0.53 |

MVC: mean corpuscular volume, RDW: red-cell distribution width, NLR: neutrophil-to-lymphocyte ratio; MPV: mean platelet volume, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. *n = 20 vs. 196, **n = 24 vs. 207 inactive and stable disease groups, respectively.
higher when compared to the cases of stage 1, while high NLR values were also reported to be significantly correlated with one-year disease progression [20]. The authors indicated a NLR cutoff value of 3.20 (80.0% sensitivity and 76.7% specificity) to predict the disease progression in sarcoidosis patients [20].

NLR, which shows the changes in both neutrophils (main triggers of inflammatory processes and thrombosis) and lymphocytes (acting more specifically in specific immunity rather than tissue damage), is considered a good prognostic marker especially for tissue damage due to inflammation [7,13,21–23]. Hence, given that sarcoidosis is a multisystemic inflammatory granulomatous disease, the association of high NLR determined at the initial diagnosis with an advanced disease stage, and the active clinical status in our sarcoidosis patients seems notable since both stage III disease and extra-pulmonary involvement were reported to be associated with the chronic and progressive course and increased likelihood of relapse [24–26].
Nonetheless, in a past study with 75 sarcoidosis patients, NLR values were reported to be significantly higher at stage-2 and stage-3 than at stage –1 and stage –4, while the authors also noted no significant association of high NLR with pulmonary PH, spontaneous remission, response to treatment or prognosis [6].

We have previously reported in a study with 1300 sarcoidosis patients that 73.0% of patients had NLR ≥ 2, while 27.0% had NLR < 2 at the time of presentation to the hospital, along with correlation of NLR values with inflammatory markers such as PLT/MPV, ESR, and CRP [19]. Similarly, a NLR cutoff value of >3.5 (sensitivity: 50%, specificity: 78%) was reported to be associated with a more intense inflammatory response and thus increased likelihood of sarcoidosis to be accompanied with pulmonary hypertension, while higher NLR also remained an independent predictor of pulmonary hypertension in multivariate analysis [11]. In addition, in a retrospective past study with 50 patients with chronic hypersensitivity pneumonia (HP), 20 patients with acute HP and 70 control subjects, NLR cutoff values of ≥2.76 and ≥2.15 were reported to discriminate between patients and controls and between acute and chronic HP, respectively [18].

In a retrospective analysis of bronchoalveolar lavage (BAL) samples from the 167 interstitial lung disease (ILD) patients, including those with sarcoidosis, HP, and idiopathic pulmonary fibrosis (IPF), the authors reported a NLR threshold value of 0.48 (73% sensitivity and 63% specificity) to discriminate between sarcoidosis and other ILDs, while NLR was also correlated negatively with forced vital capacity (FVC) and forced expiration volume in 1 second (FEV1) percentages and positively with composite pulmonary index (CPI) score [27]. In another study, the mean NLR value was reported to be higher in tuberculosis cases compared to the sarcoidosis cases, while a NLR cutoff value of ≥2.55 (79% sensitivity and 69% specificity) was reported to discriminate between sarcoidosis and tuberculosis [16].

In the case of HP, NLR was reported to decrease in the chronic period compared to the acute period, and this was related to the gradual decrease in the granulomas and inflammation in the lung and their replacement by fibrosis (chronic/fibrotic HP) as the disease progresses to chronic HP [18,28]. Notably, NLR was also reported to predict the exacerbations and severity of COPD [29], while the increase in NLR was reported to be related to all-cause mortality in acute pulmonary embolism [30].

Accordingly, in line with previous studies that indicated the utility of NLR in predicting the risk of parenchymal involvement, radiological extent and progression of disease [7,10,11,17,20], as well as the development of pulmonary hypertension [11] and hypersensitivity pneumonia [18] in sarcoidosis patients, our findings revealed the utility of NLR as a simple readily available and low-cost biomarker for advanced disease stage and active clinical status in patients with sarcoidosis.

Notably, RDW values were also significantly higher in patients with active vs. stable sarcoidosis in the current study, while there was a non-significant tendency for higher RDW values in the case of the advanced disease stage. These findings seem notable given that in the past study with 138 sarcoidosis patients, baseline, and follow-up values of RDW were reported to be significantly higher in patients with stage 4 than other stages, while significant increase in RDW levels from baseline was noted in follow up of patients with progressive disease but not in follow up those with stable disease [31].

The major limitations of this study seem to be the retrospective single-center design and relatively low sample size due to the rarity of the disease, which prevents generalization of our findings to the overall sarcoidosis patient population.

In conclusion, our findings indicate the potential utility of on-admission NLR values to predict advanced disease stage and to discriminate between active and stable disease in patients with sarcoidosis. Measured via a simple, readily available, and low-cost peripheral blood test, NLR may be a useful marker for monitoring disease activity and disease progression in sarcoidosis patients. Future prospective studies with larger samples are needed to justify the prognostic significance of inflammatory markers in sarcoidosis patients.

Disclosure of financial/other effects of conflict of interest

The authors have no relevant conflicts of interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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