The clinical significance of hematologic parameters in patients with sarcoidosis

Nigar Dirican[1], Ceyda Anar[2], Sule Kaya[1], Haci Ahmet Bircan[1], Huseyin Halil Colar[2] and Munire Cakir[1]

1 Department of Chest Diseases, Medical Faculty, Suleyman Demirel University, Isparta, Turkey
2 Department of Chest Diseases, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Izmir, Turkey

Abstract

Background: Sarcoidosis is a multisystemic inflammatory granulomatous disease of unknown etiology. No suitable biomarkers are available to evaluate the prognosis of this disease, which still has an unpredictable clinical course. The aim of this study was to evaluate the potential clinical usefulness of hematologic markers.

Materials and Methods: We investigated 172 subjects: 116 patients with sarcoidosis and 56 healthy individuals at Suleyman Demirel University and Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital. Complete blood count, demographics and pulmonary function test data from sarcoidosis patients between 2008 and 2013 were evaluated and collated retrospectively. The cut-off values were determined by calculating the neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) of the patients.

Results: The cut-off values were determined as 2 and 8.95 for NLR and MPV, respectively. NLRs were significantly higher in sarcoidosis patients than in healthy controls ($P < 0.001$) and were directly correlated with erythrocyte sedimentation rate (ESR) levels ($R = 0.183$, $P = 0.017$). Receiver operator characteristic (ROC) curve analysis revealed a 0.83 [confidence interval (CI) 68.8%–88.4%] area under the curve, 80% sensitivity and 59% specificity at the cut-off of NLR. Higher NLRs (≥2) were detected in patients with sarcoidosis than in the control group ($P < 0.001$). Also, high NLRs were more frequent in patients with extrapulmonary involvement ($P = 0.031$). MPV values were not different between control and patient groups.

Conclusions: NLR may be a biomarker with good sensitivity that is easily detected in serum. It can be proposed in clinical practice to identify a patient's prognosis. However, large prospective studies are required to further demonstrate the prognostic significance of these values.

Please cite this paper as: Dirican N, Anar C, Kaya S, Bircan HA, Colar HH and Cakir M. The clinical significance of hematologic parameters in patients with sarcoidosis. *Clin Respir J* 2016; 10: 32–39. DOI:10.1111/crj.12178.

Key words
sarcoidosis – neutrophil-to-lymphocyte ratio – prognosis – stage

Correspondence
Nigar Dirican, MD, Department of Chest Diseases, Suleyman Demirel University, Medical Faculty, 32260 Isparta, Turkey.
email: nigardirican@yahoo.com

Received: 07 March 2014
Revision requested: 15 June 2014
Accepted: 22 June 2014

DOI:10.1111/crj.12178

Authorship and contributorship
Principal author, Nigar Dirican, performed the research, collected and analyzed the data and wrote the paper. All the other authors contributed to the design of the study, the interpretation of results and the revision of the manuscript.

Ethics
The study was conducted according to good clinical practice and the Declaration of Helsinki. Protocol approval was obtained from an independent ethics committee at Suleyman Demirel University. All patients provided written informed consent.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Introduction

Sarcoidosis is a multisystemic inflammatory granulomatous disease of unknown origin, characterized by accumulation of activated proliferating T-lymphocytes and mononuclear phagocytes in the involved organs (1, 2). It may involve multiple organs, including lungs, lymph nodes, joints, skin and eyes. Lung involvement occurs in over 90% of patients with sarcoidosis (3). Two thirds of patients with sarcoidosis generally have a remission within a decade after diagnosis, with little or no consequence; remission occurs in more than half of patients within 3 years. Unfortunately, up to a third of patients have

unrelenting disease, leading to clinically significant organ impairment. There are no data on the indications for specific tests or the optimal frequency of monitoring disease activity in sarcoidosis (4). The clinical expression, natural history and prognosis of sarcoidosis are unpredictable, and no reliable indicators of clinical outcome is available. Proposed biomarkers include many cytokines, chemokines and macrophage- or lymphocyte-derived mediators, such as angiotensin-converting enzyme (ACE), neopterin, interleukin-2 receptor (IL-2R) and lysozyme, but there is no single reliable biomarker with unequivocal, proved prognostic value (5–9).

Leukocyte count and its subtypes are also well-known inflammatory markers (10, 11). In recent years, there have been some studies investigating the potential role of leukocyte subtype ratios during the inflammatory process of chronic diseases (12, 13). The ratio of absolute neutrophil count to lymphocyte count [neutrophil-to-lymphocyte ratio (NLR)] was introduced as a cost-effective potential inflammatory marker that has prognostic and predictive values in systemic inflammatory diseases and cancer (12–15). Evidence of the significance of NLR as an inflammation marker has been increasing. Changes in peripheral blood, such as neutrophilia, lymphopenia and thrombocytosis, have been defined as responses to systemic inflammation (16–19). Evidence has accumulated, suggesting an important role for mean platelet volume (MPV) as a marker of inflammation, disease activity and efficacy of anti-inflammatory treatment in several chronic inflammatory disorders (20). Red-cell distribution width (RDW) is usually assessed as part of the hemogram to obtain information about variability in the size of circulating erythrocytes (21). It has been previously proposed that an elevated RDW is caused by an underlying state of inflammation that induces changes in erythropoiesis, red blood cell circulation half life and red blood cell membrane deformability (22, 23).

Studies on the role of serum biomarkers in the diagnosis and monitoring of sarcoidosis are limited in the literature. Also, to our knowledge, detailed examination of the various hematologic parameters (e.g. NLR) in the peripheral blood in sarcoidosis patients has not been described. Thus, the primary goal of this study was to identify new biomarkers of sarcoidosis. To achieve this objective and to compare the measurement with an appropriately matched control population, we selected NLR and other inflammation parameters [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), MPV and RDW] in patients with sarcoidosis.

Material and methods

We investigated 172 subjects – 116 patients with sarcoidosis and 56 healthy individuals – at Suleyman Demirel University and Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital from January 2008 to December 2013. The diagnosis of sarcoidosis was established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs of non-caseating epithelioid-cell granulomas in the absence of organisms or particles. Patients with fever, erythema nodosum, arthralgias and bilateral hilar lymphadenopathy were accepted to have Löfgren's syndrome and sarcoidosis without histopathological confirmation. In addition, a ratio of cluster of differentiation (CD)4/CD8 of >3.5 was used as a criteria for diagnosis on bronchoalveolar lavage (24).

The hospital participating in the present study has been employing an automatization system since 2008, and complete blood count data were obtained for all patients as baseline data. Furthermore, age, sex, clinicopathological characteristics, chest radiographs, stage, laboratory values, serum ACE levels and pulmonary function parameters were recorded for these patients. Patients with active infection (high fever, classical symptoms and signs of infection in systems such as the upper and lower respiratory system and urinary system, identification of microorganisms in cultures of serous effusions and radiologic signs of infection), active bleeding, blood transfusion within the last 3 months, chronic inflammatory disease (rheumatic disease, vasculitis, inflammatory bowel disease, chronic respiratory disease, chronic heart disease, etc.) or autoimmune disease with steroid treatment were excluded from the study. Chest radiographs in patients with sarcoidosis have been classified into four stages: 0, normal chest radiographic findings; I, bilateral hilar adenopathy with normal lung parenchyma; II, bilateral hilar adenopathy with pulmonary infiltrates; III, pulmonary infiltrates without hilar adenopathy; and IV, pulmonary fibrosis/fibrocystic parenchymal changes (25). Written informed consent was obtained from each of the healthy individuals who comprised the control group.

Complete blood and inflammatory-marker counts

Complete blood counts were measured by the method of flow cytometry (Beckman Coulter LH 780 Analyzer; Beckman Coulter Inc., Miami, FL, USA). Venous blood

samples were drawn into tubes containing ethylenediaminetetraacetic acid for the measurement of hematological parameters before treatment. Hematological parameters (leukocytes, neutrophils, lymphocytes, NLR, MPV and RDW) were recorded at the time diagnosis was made. The NLR was constructed as follows: NLR = neutrophil count to lymphocyte count. CRP was determined by the turbidimetric method (Toshiba ACCUTE TBA-40FR; Toshiba Medical Systems, Tokyo, Japan). Peripheral blood was obtained at the time of diagnosis. ACE was measured by spectrophotometric methods. ESR was measured by spectrophotometric assay (Alifax test – 1 THL, 950 nm).

Pulmonary function tests (PFT)

Lung function was tested using a pneumotachometric spirometer (CustovitM, Custo Med, Munich, Germany) with subjects in the sitting position. The highest value of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), from at least two technically satisfactory maneuvers differing by less than 5%, was recorded. Predicted values were obtained from Quanjer *et al.* (26).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows v20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to determine whether or not these were normally distributed. Continuous variables were expressed as mean [standard deviation (SD)] or median (interquartile range) according to distribution state. Categorical variables were expressed as numbers and percentages. The chi-squared test was used to compare proportions in different groups. The Student's *t*-test or the Mann–Whitney *U*-test was used to compare the two independent groups according to distribution state. The Kruskal–Wallis test was used for comparing more than two independent groups for non-normal distributed variables. In cases where the Kruskal–Wallis test yielded statistical significance, post hoc analysis was performed to identify the groups that showed differences by a Bonferroni-corrected Mann–Whitney *U*-test. Regression tree analysis of censored data was used to determine the cut-off of the NLR and MPV. The correlation coefficients and their significance between non-normally distributed variables (NLR and other laboratory values: ESR, MPV, CRP and ACE) were analyzed using the Spearman test. Linear regression analyses were performed to identify possible association of NLR as a dependent variable with potential confounding factors among three groups with stepwise method. Two-tailed *P* values of less than 0.05 were considered statistically significant.

Ethics

The study was conducted according to good clinical practice and the Declaration of Helsinki. Protocol approval was obtained from an independent ethics committee at Suleyman Demirel University. All patients provided written informed consent (Ethics Committee acceptance number 100 and date May 4, 2014).

Results

While the diagnosis was based on histopathological findings in 94 out of 116 (81%) patients, a clinico-radiological diagnosis was established in 22 patients. Overall mean age was 47.8 years, and 73.3% ($n = 85$) of the patients were women. The stage 0 group had a mean age of 46.7 and women of $n = 2$ (2.4% of total); the stage I group had a mean age of 47 and women of $n = 39$ (45.9% of total); the stage II group had a mean age of 48 and women of $n = 43$ (50.6% of total); and the stage III group had a mean age of 48 and women of $n = 1$ (1.2% of total). Five (2.9%) patients were classified as stage 0, 51 (29.7%) patients were classified as stage I, 57 (57%) patients were classified as stage II, and 3 (1.7%) patients were classified as stage III sarcoidosis. There were no stage IV patients. The sarcoidosis group was divided into two subgroups according to the stage of the patients (stage 0–I vs stage II–III). The characteristics and laboratory findings of participants from the three groups (control, stage 0–I and stage II–III) are found in Table 1.

Laboratory findings

There was a significant difference in results of NLR and sedimentation ($P < 0.001$ and $P < 0.01$, respectively) among all three groups (Table 1, Figs 1–2). There was a significant difference in MPV values between the control group and all sarcoidosis patients regardless of stage ($P = 0.030$, Table 1). No difference was found in the levels of RDW, CRP and ACE between groups ($P = 0.725$, $P = 0.634$, and $P = 0.239$, respectively). The cut-off values for NLR and MPV for predicting a sarcoidosis diagnosis were determined as 2.0 and 8.95, respectively. Receiver operator characteristic (ROC)

Table 1. Characteristics, Laboratory Findings and Pulmonary Function Tests of Study Groups

	Control	Sarcoidosis (stage 0,1)	Sarcoidosis (stage 2,3)	*P*	Sarcoidosis (all stage)	*P*†
Number	56	56	60		116	
Age, year, mean (SD)	49 (12.1)	47.2 (11.15)	48.3 (10.9)	NS	47.81 (11.0)	NS
Sex, female, *n* (%)	41 (23.8)	41 (23.8)	44 (25.6)	NS	85 (49.4)	NS
Laboratory findings*						
NLR	1.82 (1.22)	2.49 (1.24)	3.02 (1.47)	<0.001	2.67 (1.27)	<0.001
MPV, fl	8.1 (1.1)	8.3 (1.5)	8.3 (1.3)	0.091	8.3 (1.4)	0.030
RDW, fl	14.2 (1.9)	14.4 (2.3)	14.5 (2.1)	0.725	14.0 (2.2)	0.433
CRP, mg/dl	3.3 (3.9)	2.5 (5.5)	3.2 (8.4)	0.634	3.05 (6.2)	0.699
ESR mm/h	11 (11)	20 (36)	26 (34)	<0.001	22 (37)	<0.001
ACE U/L	NA	25 (78)	63 (94.4)	0.239	NA	
Pulmonary function test, mean (SD)						
FEV1, %	NA	84.6 (15.2)	80.6 (14.3)	0.055		NA
FEV1, mL	NA	2446 (749)	2160 (540)	0.054		NA
FEV1/FVC, %	NA	94.8 (13.7)	93.3 (11.4)	0.600		NA
DLCO	NA	77.4 (7.8)	70 (12.1)	0.004		
Clinical symptoms, *n* (%)						
Fever	NA	8 (6.9)	7 (6.0)	0.784		NA
Arthritis/arthralgia	NA	12 (10.3)	9 (7.8)	0.471		NA
Dyspnea	NA	5 (4.3)	26 (22.4)	<0.001		NA
Cough	NA	16 (13.8)	38 (32.8)	<0.001		NA
Weakness	NA	7 (6.0)	26 (22.4)	<0.001		NA
Erythema nodosum	NA	10 (8.6)	9 (7.8)	0.803		NA
Weight loss	NA	2 (1.7)	6 (5.2)	0.274		NA
Night sweat	NA	2 (1.7)	10 (8.6)	0.030		NA
Chest pain	NA	2 (1.7)	5 (4.3)	0.441		NA

$P < 0.05$ was statistically significant.

*Data are median (interquartile range) unless otherwise indicated.

†All stage sarcoidosis patients vs control.

NLR, neutrophil-to-lymphocyte ratio. MPV, mean platelet volume (fl) = [plateletcrit(%) / plateletcount (×109/l)] × 105. CRP, C-reactive protein. ESR, erythrocyte sedimentation rate. ACE, angiotensin converting enzyme. FEV1, forced expiratory volume in 1 s. FVC, forced vital capacity. DLCO, diffusing capacity of lung. NA, not applicable. SD, standard deviation.

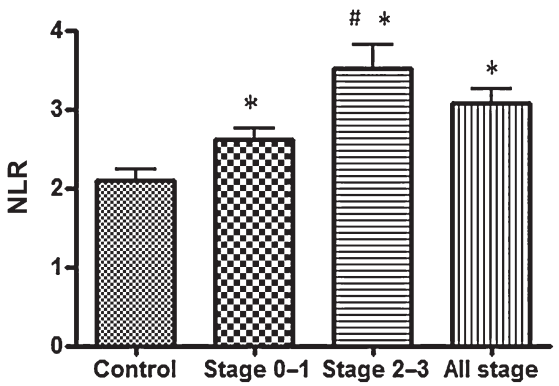

Figure 1. Neutrophil-to-lymphocyte ratio (NLR) in patients with stage 0–1, stage 2–3, all stage sarcoidosis and healthy individuals. Data are presented as mean ± standard error. *$P < 0.001$, when compared with sarcoidosis (stage 0–1, stage 2–3, all stage) and healthy individuals; #$P < 0.05$, when compared with sarcoidosis stage 0–1 and stage 2–3. $P < 0.05$ was statistically significant.

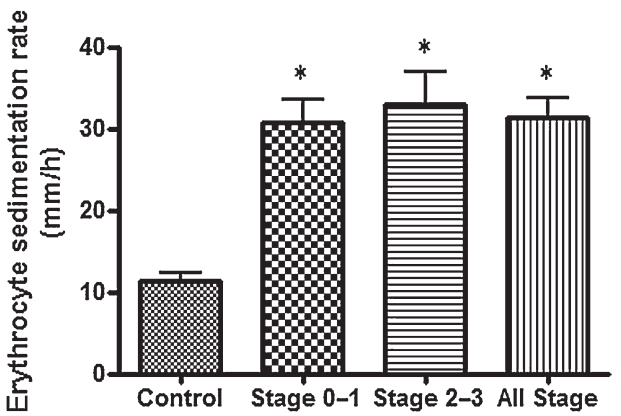

Figure 2. Erythrocyte sedimentation rate in patients with stage 0–1, stage 2–3 and all stage sarcoidosis, healthy individuals. Data are presented as mean ± standard error. *$P < 0.001$, when compared with sarcoidosis (stage 0–1, stage 2–3, all stage) and healthy individuals; $P < 0.05$ was statistically significant.

curve analysis revealed a 0.83 (CI 68.8–88.4) area under the curve, 80% sensitivity and 59% specificity with the cut-off of NLR (Fig. 3). The value of cut-off for MPV revealed an area under the curve of 0.60 (CI 51.4–69.0), 34% sensitivity and 85% specificity (Fig. 4). Positive predictive values and negative predictive values for NLR and MPV were 80% and 83%, and 58% and 39%, respectively.

The study group was divided into two groups according to NLR and MPV [high NLR (≥2.0) and low NLR (<2.0); high MPV (≥8.95) and low MPV (<8.95)]. The level of high NLR in patients with sarcoidosis was higher than in the control group, and it was also found that as the stage increased, the number of patients with high NLR increased (Table 2). The ratio of stage II–III patients with high MPV was higher than in the control group ($P = 0.018$). When all of the sarcoidosis patients were evaluated together, the ratio of high MPV was higher than in the control group ($P < 0.001$).

PFT

No significant difference was present in PFT results between the sarcoidosis groups (Table 1).

Correlations between NLR and other parameters

The clinical symptoms of dyspnea, cough, weakness and night sweats were more frequently observed in radiologically advanced-stage patients with sarcoidosis, but there was no difference in terms of other symptoms (Table 1). When the correlation between high-NLR and low-NLR patients and clinical symptoms was evaluated, symptoms associated with pulmonary involvement, such as cough and dyspnea, were seen more frequently in high-NLR patients ($P = 0.008$ and $P = 0.032$, respectively). The other symptoms were similarly observed more frequently in high-NLR patients, but this did not reach statistical significance (Table 3). While extrapulmonary involvement was seen more often in high-NLR patients ($P = 0.031$, Table 3), this difference revealed significance especially in skin-involvement patients ($P = 0.032$, Table 3). There was a statistically significant positive correlation between increased sedimentation and NLR when the stage of the disease was increased ($R = 0.183$, $P = 0.017$; Fig. 5). There was no correlation between NLR with MPV and the level of RDW, CRP and ACE (respectively: $R = 0.026$, $P = 0.731$; $R = 0.089$, $P = 0.236$; $R = 0.138$, $P = 0.140$).

Stage, sex, age, CRP, ESR, ACE, PFT, clinical symptoms, NLR and other hematologic parameters were different among the groups, and these were entered into linear regression with a stepwise method. Among these, stage ($\beta = 0.269$, $P = 0.006$) and ESR ($\beta = 0.24$, $P < 0.001$) were dependently associated with NLR values.

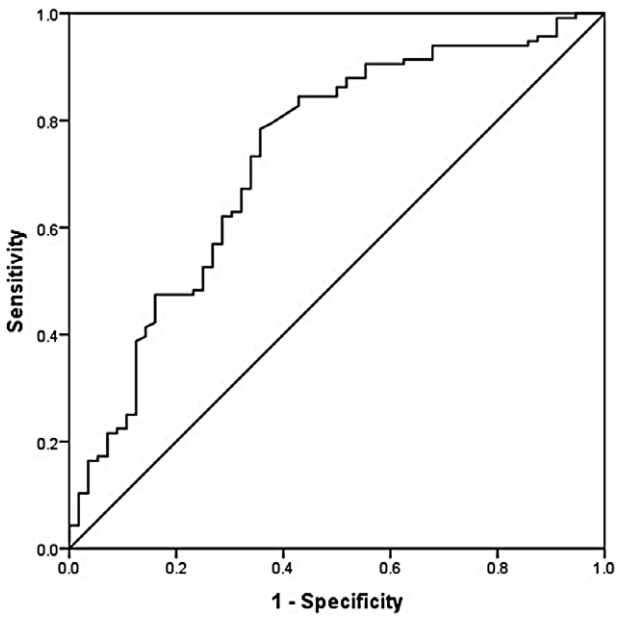

Figure 3. Receiver operator characteristic curve showing specificity and sensitivity percentages of neutrophil-to-lymphocyte ratio (NLR) in sarcoidosis patients. Area under the curve 0.83, NLR cut-off value 2, sensitivity 80.1%, specificity 59.1%.

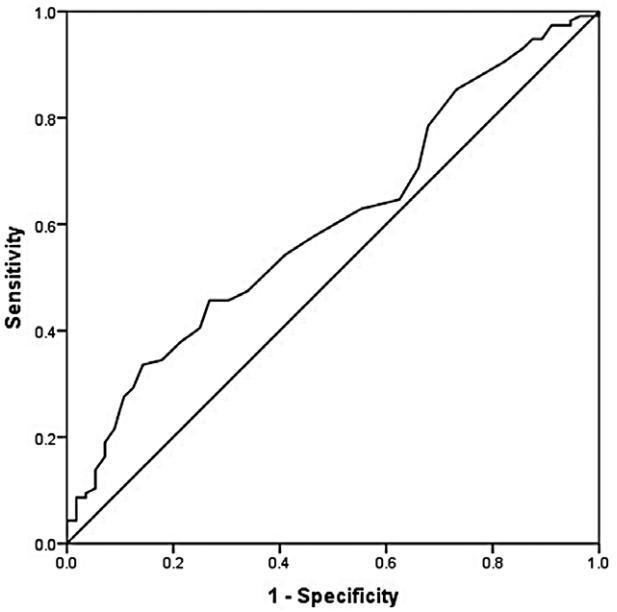

Figure 4. Receiver operator characteristic curve showing specificity and sensitivity percentages of mean platelet volume (MPV) in sarcoidosis patients. Area under the curve 0.60, MPV cut-off value 8.95, sensitivity 33.6 %, specificity 85%.

Table 2. The relationship between NLR, MPV and stage in patients with sarcoidosis and control group. High NLR: The value of NLR is 2.0 or higher than 2.0. Low NLR: The value of NLR is less than 2.0. High MPV: The value of MPV is 8.95 or higher than 8.95. Low MPV: The value of MPV is less than 8,95. $P < 0.05$ was statistically significant.

	Lown *n* (%)	High *n* (%)	*P*
NLR			
Control vs stage 0–1	32 (57.1) vs 19 (16.3)	24 (42.9) vs 37 (31.9)	<0.05
Control vs stage 2–3	32 (57.1) vs 4 (3.5)	24 (42.9) vs 56 (48.3)	<0.001
Stage 0–1 vs stage 2–3	19 (16.3) vs 4 (3.4)	37 (31.9) vs 56 (48.2)	<0.05
Control vs all stage	32 (57.1) vs 23 (19.9)	24 (42.9) vs 93 (80.1)	<0.001
MPV			
Control vs stage 0–1	48 (85.6) vs 42 (36.2)	8 (14.2) vs 18 (15.6)	P:0.175
Control vs stage 2–3	48 (85.6) vs 35 (30.1)	8 (14.2) vs 21 (18.1)	<0.05
Stage 0–1 vs stage 2–3	42 (36.2) vs 35 (30.1)	18 (15.6) vs 21 (18.1)	0.860
Control vs all stage	48 (85.6) vs 77 (66.3)	8 (14.2) vs 39 (33.7)	<0.05

Discussion

In this study, hematological parameters were evaluated in sarcoidosis patients, classified according to clinical phenotype and compared with a group of healthy controls. NLRs were significantly higher in sarcoidosis patients than in controls, with a high statistical difference. We found that when the stage of sarcoidosis increased, the ratio of NLR increased. Symptoms such as dyspnea and cough, and the probability of extrapulmonary disease, were associated with high NLR. Also, there was a positive correlation between NLR and ESR values with extrapulmonary involvement. The level of MPV was higher in the study group than in the control group, but there was no significant difference between stages. The value of NLR was of higher sensitivity and lower specificity than the value of MPV according to ROC curve analysis. No difference was found between the sarcoidosis and control groups for the value of RDW.

Some parameters of sensitivity and specificity values were determined in the sarcoidosis patients. The sensitivity and specificity of ACE, IL-2, serum amyloid A and high-sensitivity CRP as bioindicators were 68% and 75%, 64% and 88%, 95% and 37% and 91% and

Table 3. The relationship between neutrophil-to-lymphocyte ratio (NLR) and clinical symptoms and extrapulmonary disease. High NLR; the patient with NLR values of 2.0 or higher. Low NLR; the patient with NLR values less than 2.0. $P < 0.05$ was statistically significant

	Low NLR, *n* (%)	High NLR, *n* (%)	*P*
Clinical symptoms			
Fever	4 (3.4)	11 (9.5)	0.478
Arthritis/arthralgia	5 (4.3)	16 (13.8)	0.615
Dyspnea	4 (3.4)	39 (33.6)	0.032
Cough	5 (4.3)	49 (42.2)	0.008
Weakness	6 (5.2)	27 (23.3)	0.780
Erythema nodosum	5 (4.3)	14 (12.1)	0.440
Weight loss	1 (0.9)	7 (6.0)	0.592
Night sweat	3 (2.6)	9 (7.8)	0.637
Chest pain	2 (1.7)	5 (4.3)	0.551
Extrapulmonary disease	12 (10.3)	20 (17.2)	0.031
Extrapulmonary disease site			
Liver	1 (0.9)	1 (0.9)	0.359
Eye	2 (1.7)	5 (4.3)	0.624
Skin	8 (6.9)	13 (11.2)	0.032
Lymp node	1 (0.9)	1 (0.9)	0.435

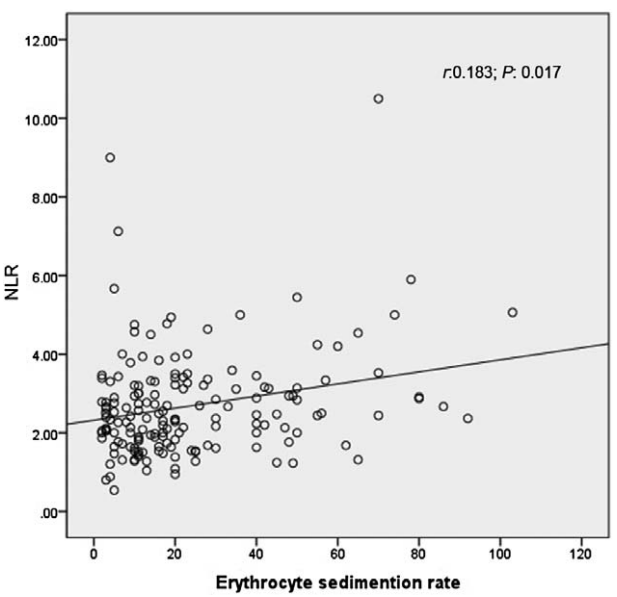

Figure 5. Correlations between neutrophil-to-lymphocyte ratio (NLR) and erythrocyte sedimentation rate (mm/h) level. r: spearman correlation coefficient, $P < 0.05$ was statistically significant.

53%, respectively, according to Rothkrantz-Kos *et al.* (27). In our study, the sensitivity and specificity of NLR and MPV were 80% and 59%, and 34% and 85%, respectively. NLR, which was similar to the parameters in this study, has a value of higher sensitivity. The positive predictive value of NLR and MPV has been identified as 80% and above. Furthermore, MPV lines were far from the ideal ROC shape, giving possibly suboptimal cut-off points (Fig. 4). NLR lines are closer to the ideal ROC shape (Fig. 3). The value of NLR was higher in patients who had a high sarcoidosis stage (Tables 1–2, Fig. 1). According to these results, it might be thought that a high value of NLR is associated with the severity of this disease. No changes in MPV values were seen as the stage increased. A previous study found that the mean CRP concentrations in sarcoidosis patients with stable or progressing disease (indicating severe disease) did not differ significantly from those in controls (28). In our study, we did not find any difference between sarcoidosis patients and the control group for the value of CRP, as in the other studies (28). Also, the level of ESR was higher in sarcoidosis patients than in the control group ($P < 0.01$, Fig. 2), as reported in the Gupta *et al.* study (29). While there was no correlation between CRP values and stage of disease, the value of ESR increased significantly when the stage increased (Table 1). According to our study, it is thought that the severity of disease may be more strongly associated with ESR than with CRP.

Since 1991, when the Ninth International Conference of Sarcoidosis approved serum ACE as a useful diagnostic and prognostic tool, it became the most widely used biomarker of sarcoidosis. However, normal serum ACE levels do not exclude sarcoidosis (30). Furthermore, this test suffers from relatively low specificity, as elevated serum ACE activity has been reported in multiple other granulomatous diseases and non-granulomatous conditions (31). The level of serum ACE was indeterminate in the control groups in our study. It was shown that the level of serum ACE increases when the stage increases; but it has not reached statistical significance ($P = 0.239$). This status can be associated partly with the lower number of patients in our study. Also, it is known that the level of serum ACE might be affected by ACE polymorphisms. In our study, the status of ACE gene polymorphism was unknown; this may explain the lack of a meaningful relationship between the level of ACE and the stage of the patient (32). It has previously been proposed that an elevated RDW is caused by an underlying state of inflammation that induces changes in erythropoiesis, red blood cell circulation half life and red blood cell membrane deformability (33). Ozsu *et al.* found in their study that in patients with stage IV sarcoidosis, baseline and follow-up values of RDW were found to be significantly higher than in the other stages, and no difference was found between the baseline and follow-up levels of RDW in the regressive and stable groups (34). Their study also showed that serial RDW follow-up may be beneficial in predicting the progression of sarcoidosis (34). In our study, no difference was found between control groups and the stage of sarcoidosis for the value of RDW ($P = 0.725$).

The importance of NLR in patients with sarcoidosis has been described for the first time in our study. The value of NLR in patients with sarcoidosis was higher than in the control group, and in patients with stage II–III disease, values of NLR were found to be significantly higher than in the other stages. In addition, extrapulmonary involvement, especially skin involvement, was more likely to be seen in patients with sarcoidosis who had a high NLR. In addition, symptoms such as cough and dyspnea were seen more frequently in high-NLR patients with sarcoidosis. This situation may be associated with parenchymal lung involvement.

Conclusions

The major limitation of the present study is its retrospective nature. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathological parameters in our patient cohort may have biased the results observed in the present study. Despite this limitation, our clinical observation shows that the NLR may be associated with pulmonary involvement and extrapulmonary involvement in patients with sarcoidosis. The NLR is an easy-to-determine, reproducible and inexpensive test. It can be easily incorporated into routine use as a prognostic factor. NLR is obviously better than other hematologic parameters of predicting the prognosis for sarcoidosis. Despite these results, prospective studies evaluating NLR in large series are required in this field.

References

1. Hunninghake GW, Costabel U, Ando M, *et al.* ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16: 149–73.
2. Yamamoto M, Sharma OP, Hosoda Y. Special report: The 1991descriptive definition of sarcoidosis. Sardoidosis. 1992;9: 33–4.
3. Kiter G, Müsellim B, Cetinkaya E, *et al.* Clinical presentations and diagnostic work-up in sarcoidosis: A series of Turkish cases (clinics and diagnosis of sarcoidosis). Tuberk Toraks. 2011;59(3): 248–58.

4. Januzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21): 2153–65.
5. Agostini C, Trentin L, Facco M, *et al*. Role of IL-15, IL-2, and their receptors in the development of T cell alveolitis in pulmonary sarcoidosis. J Immunol. 1996;157: 910–8.
6. Agostini C, Semenzato G. Cytokines in sarcoidosis. Semin Respir Infect. 1998;13: 184–96.
7. Prior C, Knight RA, Herold M. Pulmonary sarcoidosis: Patterns of cytokine release *in vitro*. Eur Respir J. 1996;9: 47–53.
8. Gurrieri C, Bortoli M, Brunetta E, Piazza F, Agostini C. Cytokines, chemokines and other biomolecular markers in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(1): 9–14.
9. Baudin B. ACE for sarcoidosis diagnosis. Pathol Biol. 2005;53: 183–8.
10. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA. 2013;309: 2353–61.
11. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. NEJM. 2003;348: 138–50.
12. Azab B, Chainani V, Shah N, McGinn JT. Neutrophil–lymphocyte ratio as a predictor of major adverse cardiac events among diabetic population: A 4-year follow-up study. Angiology. 2013;64(6): 456–65.
13. Dirican A, Ekinci N, Avci A, *et al*. The effects of hematological parameters and tumor-infiltrating lymphocytes on prognosis in patients with gastric cancer. Cancer Biomark. 2013;13(1): 11–20.
14. Ertaş G, Sönmez O, Turfan M, *et al*. Neutrophil/lymphocyte ratio is associated with thromboembolic stroke in patients with non-valvular atrial fibrillation. J Neurol Sci. 2013;324: 49–52.
15. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, Yurci A, Güven K, Yücesoy M. Neutrophil–lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal. 2013;27: 72–6.
16. Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B, Amiral J, Richter V, Wagner OF. Regulation of adhesion molecules during human endotoxemia. No acute effects of aspirin. Am J Respir Crit Care Med. 1999;159: 857–63.
17. Dionigi R, Dominioni L, Benevento A, Giudice G, Cuffari S, Bordone N, Caravati F, Carcano G, Gennari R. Effects of surgical trauma of laparoscopic vs. open cholecystectomy. Hepatogastroenterology. 1994;41: 471–6.
18. O'Mahony JB, Palder SB, Wood JJ, McIrvine A, Rodrick ML, Demling RH, Mannick JA. Depression of cellular immunity after multiple trauma in the absence of sepsis. J Trauma. 1984;24: 869–75.
19. Zahorec R. Ratio of neutrophil to lymphocyte counts – Rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102: 5–14.
20. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: A link between thrombosis and inflammation? Curr Pharm Des. 2011;17: 47–58.
21. Schweiger DJ. Red cell distribution width in sickle cell anemia. Am J Med Technol. 1981;47: 231–3.
22. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. Crit Care Med. 2011;39(8): 1913–21.
23. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133(4): 628–32.
24. Statement on sarcoidosis. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999;160: 736–55.
25. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. Br Med J. 1961;2(5261): 1165–72.
26. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. Eur Respir J Suppl. 1993;16: 5–40.
27. Rothkranz-Kos S, van Dieijen-Visser MP, Mulder PG, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. Clin Chem. 2003;49: 1510–7.
28. Ziegenhagen MW, Rothe ME, Schlaak M, Muller-Quernheim J. Bronchoalveolar and serological parameters reflecting these verity of sarcoidosis. Eur Respir J. 2003;21: 407–13.
29. Gupta D, Rao VM, Aggarwal AN, Garewal G, Jindal SK. Haematological abnormalities in patients of sarcoidosis. Indian J Chest Dis Allied Sci. 2002;44(4): 233–6.
30. Bargagli E, Mazzi A, Rottoli P. Markers of inflammation in sarcoidosis: Blood, urine, BAL, sputum, and exhaled gas. Clin Chest Med. 2008;29(3): 445–58.
31. Geyer AI, Kraus T, Roberts M, Wisnivesky J, Eber CD, Hiensch R, Moran TM. Plasma level of interferon γ induced protein 10 is a marker of sarcoidosis disease activity. Cytokine. 2013;64(1): 152–7.
32. Sharma P, Smith I, Maguire G, Stewart S, Shneerson J, Brown MJ. Clinical value of ACE genotyping in diagnosis of sarcoidosis. Lancet. 1997;349: 1602–3.
33. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected out patients. Arch Pathol Lab Med. 2009;133(4): 628–32.
34. Ozsu S, Ozcelik N, Oztuna F, Ozlu T. Prognostic value of red cell distribution width in patients with sarcoidosis. Clin Respir J. 2014;9. doi: 10.1111/crj.12101.