

## THE IMPORTANCE OF PET/CT FINDINGS AND HEMATOLOGICAL PARAMETERS IN PREDICTION OF PROGRESSION IN SARCOIDOSIS CASES

Kemal Can Tertemiz<sup>1</sup>, Aylin Ozgen Alpaydin<sup>1</sup>, Volkan Karacam<sup>2</sup>, Seda Mersin<sup>1</sup>, Recep Bekis<sup>3</sup>, Can Sevinc<sup>1</sup>

<sup>1</sup>Pulmonary Diseases, Dokuz Eylul University Medical Faculty, Izmir, Turkey; <sup>2</sup>Thoracic Surgery, Dokuz Eylul University Medical Faculty, Izmir, Turkey; <sup>3</sup>Nuclear Medicine, Dokuz Eylul University Medical Faculty, Izmir, Turkey

**ABSTRACT.** *Aim:* We aimed to reveal the correlation of NLR rate, RDW and MPV values and with the findings of PET/CT regarding the prediction of disease progression and the clinical characteristics. *Materials and methods:* The treatment naive sarcoidosis cases, of whose PET/CT have been taken due to mediastinal lymphadenopathy of whose diagnosis have been confirmed by biopsy, were included in the study. Hematological parameters, clinical, radiological and PET/CT findings are evaluated. *Results:* 40 sarcoidosis and 40 healthy control cases were included in the study. NLR, RDW, MPV and the sedimentation values in the sarcoidosis group were determined statistically significantly higher. In patients having parenchymal involvement in PET/CT, the values of FVC%, DLCO, DLCO%, DLCO/VA and DLCO/VA% were determined significantly lower. High NLR and PET/CT LAP SUVmax values and low DLCO% values are statistically significantly correlated with one-year disease progression. For predicting the progression, for the NLR cut-off value 3.20, the area under the curve was determined as 0.79 (CI 62.2-96.5), sensitivity as 80.0%, specificity as 76.7% and for the PET/CT SUVmax cut-off value 9.5, the area under the curve was determined as 0.71 (CI 46.6-95.9), sensitivity as 70.0%, specificity as 82.1%. *Conclusion:* We determined that the values observed in routine hematologic examinations such as NLR, RDW and MPV, were high in sarcoidosis cases. In addition, the values of NLR, DLCO% and PET/CT SUVmax might be used in predicting the progression. At the same, once again we showed that the lung parenchyma involvement in PET/CT correlates with many pulmonary function parameters. (*Sarcoidosis Vasc Diffuse Lung Dis* 2017; 34: 242-250)

**KEY WORDS:** sarcoidosis, NLR, MPV, RDW, PET/CT, disease progression

### INTRODUCTION

Sarcoidosis is defined as an idiopathic multisystem granulomatous disease. As a pathological sign, the non-caseating granulomas containing epithelioid

and multi-nuclear giant cells, are characteristic for sarcoidosis (1).

Lungs and thoracic lymph nodes are the most commonly involved sites. Extrathoracic involvement frequency ranges between 25-50% and is usually associated with thoracic involvement (2).

Sarcoidosis can be asymptomatic or can be diagnosed by incidentally taken chest radiography. More commonly, symptoms are associated with the involved organ or the extensity of the involvement of the system (3).

Prognosis is generally good. Spontaneous remission is seen in 2/3 of the cases and the rest becomes

Received: 20 March 2016

Accepted after revision: 23 January 2017

Correspondence: Dr. Kemal Can Tertemiz

Dokuz Eylul University Medical Faculty,

Department of Pulmonary Diseases,

Balcova, Izmir, Turkey 35340

Tel: +90 232 412 3809

Fax: +90 232 259 9723

E-mail: kemal.tertemiz@deu.edu.tr; tkemalcan@yahoo.com

chronic. Slow progression is observed in 10-15% of the cases which may progress to lung fibrosis. The most frequent causes of death are pulmonary fibrosis, as well as cardiac and neurological involvement (1).

Angiotensin converting enzyme (ACE) is generally secreted from sarcoid granulomas and its serum level is used in the diagnosis and treatment decision (3). However, only in the 60% of the patients with chronic sarcoidosis, the serum ACE level is determined as high. In addition, the disease severity is not associated with progression, clinical outcome and response to treatment (4).

The staging of sarcoidosis based upon to the chest radiography, which the modified Scadding staging system is used. This staging system has a prognostic importance. While 90% spontaneous resolution is seen at stage 0, sarcoidosis diagnosis rate is approximately 20% at stage 3 (5).

PET/CT (Positron Emission Tomography - Computed Tomography), besides showing the mediastinal lymph node involvement, it can also provide information about parenchymal inflammation and fibrosis. A correlation between PET activity and pulmonary function tests has been defined. Also, serological markers such as ACE level, soluble interleukin 2 receptor correlate with the findings of PET/CT, though the sensitivity of PET/CT is higher (1).

The neutrophil/lymphocyte ration (NLR) is determined by dividing the absolute count of neutrophils by the absolute number of lymphocytes in the complete blood count. In the recent researches, it is shown that NLR can be used as an inflammation marker. There are studies showing its correlation with cancers, cardiac and pulmonary diseases (chronic obstructive pulmonary disease (COPD), tuberculosis and pneumonia) (6-12).

It has been shown that the values of RDW (red cell distribution width) and MPV (mean platelet volume) could also increase associated with the inflammation and were found higher in patients with sarcoidosis (13).

There is limited data showing the correlation of, NLR, RDW and MPV and sarcoidosis. For this purpose, depending on the basis inflammation in cases of sarcoidosis, we planned to reveal the correlation of NLR rate, RDW and MPV values and with the findings of PET/CT regarding the prediction of disease progression and the clinical characteristics.

## MATERIALS AND METHODS

The treatment naive sarcoidosis cases, of whose PET/CT have been taken due to mediastinal lymphadenopathy between the dates January 2013-January 2015, of whose diagnosis have been confirmed by biopsy, were included in the study. The exclusion criteria were, malignancy, hematological disease, active cardiac disease, active bleeding, blood transfusion within the last 3 months, chronic inflammatory and autoimmune disease (rheumatic disease, vasculitis, inflammatory bowel disease, chronic respiratory disease, etc.), and active infection. Demographic characteristics such as age, gender, pulmonary function test values, serum ACE levels, erythrocyte sedimentation rates (ESR), complete blood counts, NLR, RDW (red cell distribution width), MPV (mean platelet volume), serum calcium, symptoms, extrapulmonary involvement existence, method of diagnosis and place of diagnosis, stages according to the chest X-ray radiography, HRCT (high resolution computerized tomography), PET/CT findings of the patients at the time of the diagnosis, were recorded.

1 year after from the date that the patients were included in the study, functional and radiographic features were again evaluated. The patients with an increase in symptoms, had serious decline in pulmonary function tests and had progression in chest X-ray findings were considered as disease progression (14).

Between the dates when the patients were included in the study, the control group having the similar demographic characteristics was selected among the healthy persons who did not have malignancy, hematologic, heart, lung disease, chronic inflammatory or autoimmune disease, acute infectious disease, to whom blood transfusion has not been made in the last 3 months and who did not receive steroids or immunosuppressive treatment.

The diagnosis of sarcoidosis was established on the basis of compatible clinical and radiologic findings, supported by histological evidence of non-caseating epithelioid-cell granulomas with the absence of organisms or particles in at least one organs.

### *Complete blood counts and inflammatory-markers*

All peripheral blood samples were obtained at the time of diagnosis.

Flow cytometry was used for complete blood count (Beckman Coulter LH 780 Analyzer; Beckman Coulter Inc. Miami, FL, USA). Hematological parameters (neutrophils, lymphocytes, NLR, MPV and RDW) were recorded. The NLR was defined as follows:  $NLR = \text{neutrophil count} / \text{lymphocyte count}$ .

ACE was measured by spectrophotometric methods. ESR was also measured by spectrophotometric assay (Alifax test – 1 THL, 950 nm).

#### *Pulmonary function tests (PFT)*

PFTs were performed with Jaeger Master Screen Pneumo V452I device by a single technician. The best test among the three consecutive ones was accepted. FEV1 (Forced expiratory volume in one second), FVC (Forced vital capacity), FEV1/FVC (Percentage of FVC expelled in the first second of a forced expiration) were measured according to American Thoracic Society criteria (15). The diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Defined by ATS criteria (16).

#### *Radiology*

Chest radiographs in patients with sarcoidosis have been classified into four stages as defined before. (Stage 0: no mediastinal adenopathy or lung infiltrates; stage 1: bilateral hilar and mediastinal lymphadenopathy; stage 2: adenopathy and pulmonary infiltrates and involvement; stage 3: pulmonary infiltrates alone; and stage 4: pulmonary fibrosis) (5).

#### *PET/CT*

The patients underwent 18F-FDG PET/CT examination on a 16-slice hybrid PET/CT scanner (Philips GEMINI TF; Philips, Eindhoven, The Netherlands). They fasted for 6 h before receiving an intravenous injection of 3.7 MBq of 18F-FDG per kilogram. PET/CT acquisitions started 60 min after tracer injection. A 3-dimensional PET scan (10-12 fields of view, 1.5 min/field) and low-dose nonenhanced CT scan were acquired from the skull to the mid thigh. If deemed necessary, a total-body study was also performed. MDCT (multiple detector computed tomography) was acquired with 120 kV and with automatic, real-time dose modulation amper-

age (the baseline being 50 mA); a slice thickness of 4 mm; PET (attenuation-corrected), and combined PET/CT images were displayed for analysis on a Extended Brilliance Workplace (Philips).

18F-FDG PET/CT findings were scored as positive or negative for inflammation. The findings were considered positive in cases of increased 18F-FDG uptake above the level in blood vessels in the mediastinum or lung parenchyma, or in extrathoracic sites, including lymph nodes, visceral organs (parotid gland, liver, spleen), nasopharynx, skin, muscle, or bone. Quantitative analysis of 18F-FDG uptake in the lesion was based on maximum standardized uptake value per focus. This value was calculated as the activity concentration measured at the end of the scan and corrected for individual body weight and dose injected, as follows:  $\text{tissue activity (counts/pixel/s)} \times \text{calibration factor} / \text{injected 18F-FDG dose (MBq/kilogram of body weight)}$  (17, 18).

#### *Statistical analyses*

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) 22.0 software package. Descriptive data were given as mean and standard deviation. Categorical variables were expressed as the number of cases and the percentage value. Continuous variables were analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests to determine whether there was normal distribution. The Student's t-test and Mann-Whitney-U test were used depending on the situation of the variables i.e. normally distributed or not. The comparison of categorical variables was performed using Chi-square and Fisher's exact tests. Spearman's correlation test was used to analyze the correlation between NLR and other inflammatory markers. In order to determine the cut-off value of NLR, ROC (receiver operating characteristics) curve analysis was used. Statistical significance was set as  $P < 0.05$ .

#### *Ethics*

The study was conducted according to good clinical practice and the Declaration of Helsinki. Protocol approval was obtained from an independent local ethics committee.

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

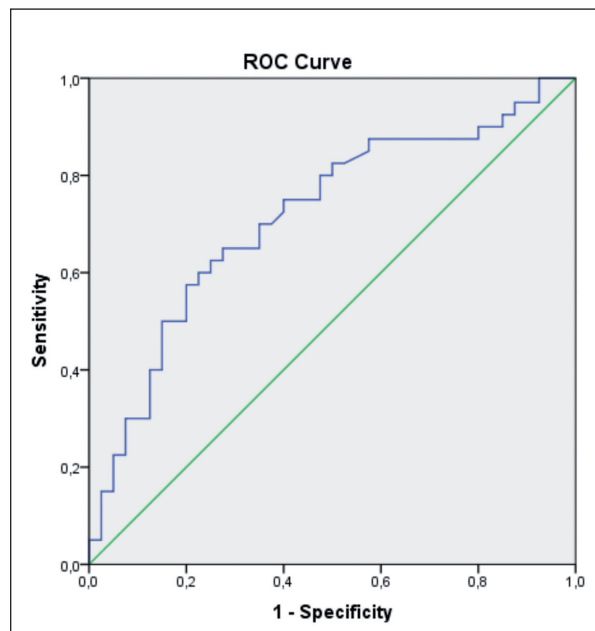
## RESULTS

40 sarcoidosis and 40 healthy control cases were included in the study. The gender and mean age of sarcoidosis patients and the control group were similar. According to the chest radiographs, 22 (55%) of the cases were stage I, 11 (27.5%) were stage II, 3 (7.5%) were stage III, and 4 (10%) were stage IV. The 26 (65%) of the patients were diagnosed by mediastinoscopy, 7 (17.5%) were diagnosed by bronchoscopy, 5 (12.5%) were diagnosed by other organ biopsies and 2 (5%) of the patients were diagnosed by lung biopsy. After one year of follow-up, stable symptoms were detected in 24 (60%) cases, progression in 10 (25%) cases and regression in 6 (15%) cases.

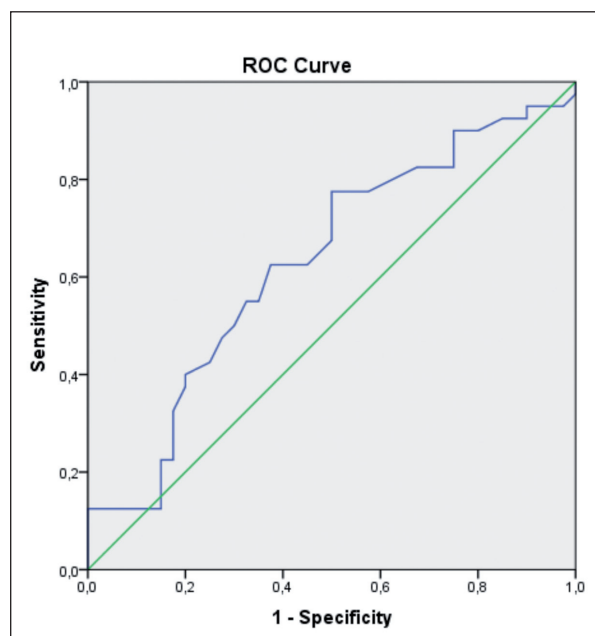
When the control group and patients with sarcoidosis have been compared; NLR, RDW, MPV and the sedimentation values in the sarcoidosis group were determined statistically significantly higher ( $p=0.012$ ,  $p=0.048$ ,  $p=0.001$ ,  $p<0.001$ , respectively). For differential diagnosis of sarcoidosis, when the NLR cut-off value was 2.50, the area under the curve was determined as 0.71 (CI 60.2-83.0), sensitivity as 70.0% and specificity as 65.0%. Receiver operator characteristic (ROC) curve for NLR is shown in figure 1. For differential diagnosis of sarcoidosis with RDW; with a cut-off value of 14.3, the area under the curve was determined as 0.63 (CI 50.7-75.3), sensitivity as 67.5% and specificity as 67.5%. ROC curve for RDW is shown in figure 2. However, the values of serum calcium and hemoglobin were determined to be similar in both groups ( $p>0.05$ ). The characteristics and laboratory findings of the sarcoidosis and control groups are shown in Table 1.

We determined that the average NLR values in sarcoidosis cases of stages 2,3 and 4 were significantly higher when compared to the cases of stage 1 (respectively  $4.82\pm 4.05$ ,  $2.59\pm 1.12$ ,  $p=0.018$ ), but the values of RDW, MPV, sedimentation, ACE and PET/CT SUVmax (Positron Emission Tomography - Computed Tomography Maximum Standardized Uptake Value) were similar ( $p>0.05$ ). No significant correlation has been determined between the hematological parameters and the symptoms ( $p>0.05$ ).

In the PET/CT, the mediastinal lymph node involvement was observed in 38 (95%) cases, and the lung parenchyma involvement was observed in 22 (55%) cases. Lung parenchyma involvement was determined in PET/CT who did not have lung paren-



**Fig. 1.** Receiver operator characteristic curve showing specificity and sensitivity percentages of NLR for discriminating sarcoidosis from controls. Area under the curve 0.71, NLR cut-off value 2.50, sensitivity 70.0% and specificity 65.0%



**Fig. 2.** Receiver operator characteristic curve showing specificity and sensitivity percentages of RDW for discriminating sarcoidosis from controls. Area under the curve 0.63, RDW cut-off value 14.3, sensitivity 67.5% and specificity 67.5%



**Table 1.** Demographic features characteristics, and hematological and functional parameters of the study population

	Sarcoidosis n=30	Control n=40	p
Age	50.3 (±14.1)	50.5 (±14.2)	>0.05
Sex, female, n (%)	27 (67.5)	27 (67.5)	>0.05
<b>Laboratory Findings (mean±SD)</b>			
NLR	3.59 (±3.02)	2.26 (±1.23)	= <b>0.012</b>
RDW (fl)	15.21 (±2.16)	14.40 (±1.37)	= <b>0.048</b>
MPV (fl)	9.22 (±1.19)	8.36 (±0.93)	= <b>0.001</b>
Hemoglobin (gr/dL)	13.08 (±1.56)	13.37 (±1.40)	>0.05
ESR (mm/H)	29.96 (±21.07)	13.62 (±6.28)	< <b>0.001</b>
ACE (U/L)	58.55 (±45.61)	NA	NA
Calcium (mEq/L)	9.48 (±0.59)	9.49 (±0.33)	>0.05
<b>Pulmonary Function Tests, (mean± SD)</b>			
FEV1, (lt)	2.21 (±0.38)	NA	NA
FEV1%	81.0 (±6.3)	NA	NA
FVC, (lt)	2.72 (±0.59)	NA	NA
FVC%	86.7 (±15.1)	NA	NA
FEV1/FVC	79.3 (±7.8)	NA	NA
DLCO ml/mmHg/min	16.89 (±4.78)	NA	NA
DLCO%	69.9 (±16.9)	NA	NA
DLCO/VA	4.10 (±0.93)	NA	NA
DLCO/VA%	85.2 (±4.1)	NA	NA
<b>Clinical symptoms, n (%)</b>			
Cough	13 (32.5)	NA	NA
Weight loss	12 (30.0)	NA	NA
Weakness	12 (30.0)	NA	NA
Chest pain	9 (22.5)	NA	NA
Dyspnea	8 (20.0)	NA	NA
Fever	5 (12.5)	NA	NA
Erythema nodosum	4 (10.0)	NA	NA

P<0.05 was statistically significant.

NLR, neutrophil-to-lymphocyte ratio. MPV, mean platelet volume (fl)=[platelet crit(%) / platelet count (×10<sup>9</sup>/l)] × 105. ACE, angiotensin converting enzyme. FEV<sub>1</sub>, forced expiratory volume in 1 s. FVC, forced vital capacity. DLCO, diffusing capacity of lung. DLCO/VA, diffusing capacity divided by the alveolar volume. NA, not applicable. SD, standard deviation

chyma involvement in HRCT in 22.2% of the cases, while no parenchymal involvement in PET/CT had lung parenchymal findings in HRCT in 38.7% of the cases (p=0.039).

Among the cases who either had nor did not have parenchymal involvement in the PET/CT, no differences were determined in terms of MPV, RDW, NLR, sedimentation, serum calcium, serum ACE levels and clinical symptoms (p>0.05). In patients having parenchymal involvement in PET/CT, the values of FVC%, DLCO, DLCO%, DLCO/VA and DLCO/VA% were determined significantly lower (p<0.05) (Table 2).

In PET/CT, apart from the lymph nodes, the pulmonary solid-organ involvement was observed in 11 (27.5%) cases (in 4 cases liver-spleen, in 3 cases arthritis, in 2 cases spleen, in 1 case liver, in 1 case

stomach). There were symptoms in 6 of these cases (54.5%), while the other cases were asymptomatic.

When the statuses of progression of the cases at the end of a year are observed, it has been determined that in the cases whose NLR and PET/CT LAP SUVmax values were high and the DLCO% value was low, statistically significantly higher rate of progression was observed (p<0.05) (Table 3). For predicting the progression, for the NLR cut-off value 3.20, the area under the curve was determined as 0.79 (CI 62.2-96.5), sensitivity as 80.0%, specificity as 76.7%. ROC curve for NLR is shown in figure 3. For predicting the progression, for the PET/CT SUVmax cut-off value 9.5, the area under the curve was determined as 0.71 (CI 46.6-95.9), sensitivity as 70.0%, specificity as 82.1%. ROC curve for PET/CT SUVmax is shown in figure 4.

**Table 2.** The association between parenchymal involvement in high resolution computed tomography and parenchymal involvement in PET/CT and pulmonary function tests

	Positive parenchymal involvement in PET/CT (n=21)	Negative parenchymal involvement in PET/CT (n=19)	p
FEV1 (lt)	2.11(±0.34)	2.32 (±0.38)	>0.05
FEV1%	79.7 (±6.9)	82.4 (±5.4)	>0.05
FVC (lt)	2.53 (±0.58)	2.92 (±0.55)	>0.05
FVC%	79.3 (±11.6)	94.8 (±14.6)	<b>=0.001</b>
FEV1/FVC	78.4 (±9.0)	80.2 (±6.2)	>0.05
DLCO ml/mmHg/min	14.98 (±5.10)	18.99 (±3.41)	<b>=0.006</b>
DLCO%	61.6 (±16.3)	79.1 (±12.4)	<b>=0.001</b>
DLCO/VA	3.62 (±0.93)	4.64 (±0.59)	<b>&lt;0.001</b>
DLCO/VA%	75.9 (±16.5)	95.4 (±13.9)	<b>&lt;0.001</b>
Positive parenchymal involvement in HRCT (n, %)	19 (61.3%)	12 (38.7%)	<b>=0.039</b>
Negative parenchymal involvement in HRCT (n, %)	2 (22.2%)	7 (77.8%)	

PET/CT, Positron emission tomography, /FEV<sub>1</sub>, forced expiratory volume in 1 s. FVC, forced vital capacity. DLCO, diffusing capacity of lung. DLCO/VA, diffusing capacity divided by the alveolar volume. HRCT, High-resolution computed tomography. Data are expressed as mean±standard deviation

**Table 3.** The association between pulmonary function tests, laboratory parameters, PET/CT findings and progression at the end of a 1-year follow-up

	Progression present (n=10)	Progression absent (n=30)	P
<b>Laboratory Findings</b>			
NLR	6.1 (±5.0)	2.7 (±1.0)	<b>=0.001</b>
RDW (fl)	14.9 (±2.2)	15.2 (±2.1)	>0.05
MPV (fl)	8.3 (±0.9)	8.3 (±0.9)	>0.05
Hemoglobin (gr/dL)	13.3 (±1.9)	13.0 (±1.4)	>0.05
ESR (mm/H)	28.7 (±15.5)	30.3 (±22.8)	>0.05
ACE (U/L)	55.9 (±36.7)	59.4 (±48.7)	>0.05
Calcium (mEq/L)	9.6 (±0.4)	9.4 (±0.6)	>0.05
<b>Pulmonary Function Test,</b>			
FEV1 (lt)	2.25 (±0.33)	2.19 (±0.39)	>0.05
FEV1%	81.7 (±7.1)	80.8 (±6.1)	>0.05
FVC (lt)	2.84 (±0.45)	2.67 (±0.63)	>0.05
FVC%	84.2 (±10.3)	87.5 (±16.5)	>0.05
FEV1/FVC	76.6 (±6.0)	80.2 (±8.2)	>0.05
DLCO ml/mmHg/min	14.5 (±6.4)	17.6 (±3.8)	>0.05
DLCO%	59.8 (±21.5)	73.3 (±13.9)	<b>=0.02</b>
DLCO/VA	4.02 (±0.99)	4.13 (±0.93)	>0.05
DLCO/VA%	85.0 (±18.8)	85.2 (±18.1)	>0.05
<b>PET/CT SUV, mean (SD)</b>			
Lymph node PET/CT SUV <sub>max</sub>	13.4 (±8.4)	7.5 (±3.4)	<b>=0.04</b>
Lung parenchyma PET/CT SUV <sub>max</sub>	3.0 (±0.6)	3.2 (±1.7)	>0.05

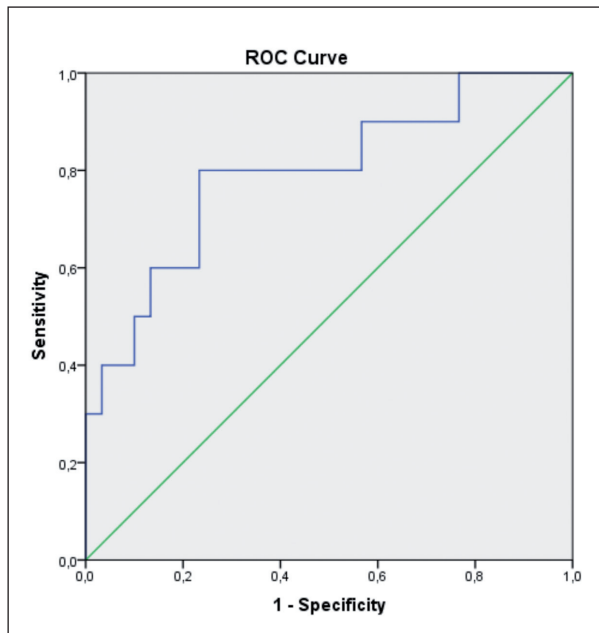
NLR, neutrophil-to-lymphocyte ratio. MPV, mean platelet volume (fl)=[platelet crit(%) /platelet count (×109/l)] × 105. ACE, angiotensin converting enzyme. FEV<sub>1</sub>, forced expiratory volume in 1 s. FVC, forced vital capacity. DLCO, diffusing capacity of lung. DLCO/VA, diffusing capacity divided by the alveolar volume. PET/CT SUV<sub>max</sub>, Positron Emission Tomography - Computed Tomography Maximum Standardized Uptake Value.

Data are expressed as mean±standard deviation.

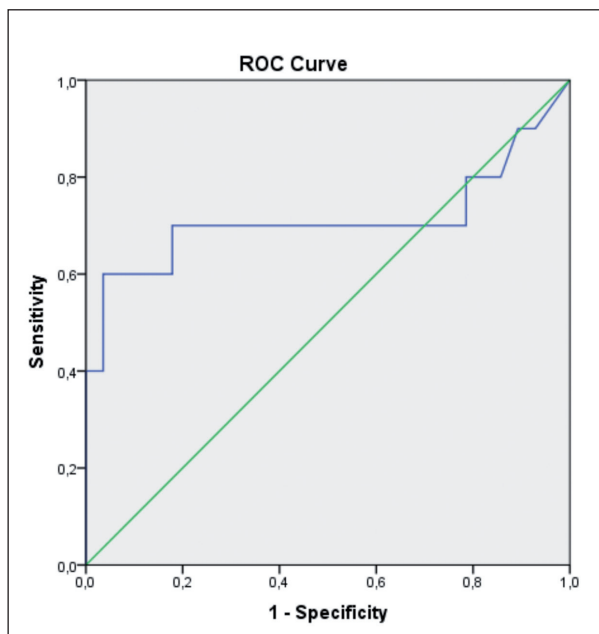
## DISCUSSION

Various serological inflammatory markers that may indicate the disease activity in sarcoidosis have

been searched. It has been shown that the neopterin and soluble interleukin-2 receptor (SIL-2) levels might rise in progressive and active diseases. However, the sensitivity and specificity of these tests are



**Fig. 3.** Receiver operator characteristic curve showing specificity and sensitivity percentages of NLR for disease progression. Area under the curve 0.79, NLR cut-off value 3.20, sensitivity 80.0 % and specificity 76.7%



**Fig. 4.** Receiver operator characteristic curve showing specificity and sensitivity percentages of PET/CT SUVmax value for disease progression. Area under the curve 0.71, of PET/CT SUVmax cut-off value 9.5, sensitivity 70.0 % and specificity 82.1%

not in ideal. It has been mentioned that more valuable data can be achieved with the addition of PET/CT findings to these tests (19, 20).

However, there is no gold standard test in sarcoidosis showing the active inflammation. In this study, we searched the correlation of hematological parameters and PET/CT findings which may show active inflammation in sarcoidosis, with the pulmonary function test parameters and clinical outcome.

In the previous studies, it has been determined that the PET/CT can show active inflammation in patients with sarcoidosis. Therefore, with respect to the disease activity, although the serum ACE level was mostly determined high in cases having PET/CT involvement compared to the cases without the involvement, the correlation of PET/CT findings with the serum ACE levels could not be revealed clearly (17, 21, 22). According to our information, the correlation between the PET/CT findings and the hematological parameters (NLR, RDW, MPV) has not been studied previously. In our study, no significant correlation has been determined between the lung parenchyma involvement and mediastinal lymph node SUVmax values in PET/CT, between the hematological parameters and serum ACE levels.

In the study of Dirican et al., the NLR, MPV and sedimentation values were found higher in cases with sarcoidosis when compared to the control group, however the RDW values were determined to be similar. Also, correlation was determined between these values and the clinical symptoms. In this study, when the NLR rate cut-off value was accepted as 2, the sensitivity was found as 80.1%, specificity as 59.1%, respectively, and when the MPV cut-off value was accepted as 8.95, the sensitivity was found as 33.6%, specificity as 85% (12). In another study, it has been shown that the NLR rate was significantly higher in cases with sarcoidosis compared to the cases with tuberculosis. When the NLR cut-off value was accepted as 2.55, in distinguishing the cases with sarcoidosis from the tuberculosis, sensitivity was determined as 79%, specificity as 69% and the diagnostic accuracy was 73% (23). In our study, the NLR, RDW, MPV and sedimentation values were determined to be statistically significantly higher in sarcoidosis cases compared to the control group. In our study, with different cut-off values, the sensitivity and specificity for NLR, MPV and RDW were determined respectively as 65.0% and 72.5%, 82.5 and

57.5, 57.5% and 67.5. However, no significant correlation has been determined between these values and the clinical symptoms.

In the sarcoidosis cases, although pathological findings are determined in the lung parenchyma in HRCT, the involvement may not be observed in the PET/CT. This situation is associated with parenchymal active inflammation. The semi quantitative HRCT scoring system was developed in order to increase the valuableness of HRCT (24). In some studies, it has been shown that the HRCT findings and pulmonary function test results were correlated with the findings of PET/CT (25, 26). In our study, while parenchymal involvement was determined in PET/CT in 22.2% of the cases who did not have lung parenchymal involvement in HRCT, in 38.7% of the cases who had lung parenchymal involvement in HRCT, no parenchymal involvement was determined in PET/CT ( $p=0.039$ ). In the studies, lower lung function tests and diffusion test values were determined in cases having the lung parenchyma involvement in PET/CT (26, 27). Similarly, also in our study, in cases having parenchymal involvement in PET/CT, the FVC% and diffusion test values were determined to be significantly lower. This finding is an another indicator that the parenchymal active disease can be demonstrated better by PET/CT compared to the HRCT.

In sarcoidosis, PET/CT is important in terms of showing the extrathoracic involvement. In the study of the Cremers et al., the extrathoracic involvement (lymph nodes, bone marrow and solid organs) was determined at the rate of 75% (27). However, in our research we found that the involvement of extrapulmonary solid organ was as 27.5%. Approximately half of these cases were asymptomatic. Therefore, PET/CT is very important in showing the silent extra thoracic involvements which could affect the treatment.

It has been shown that the PET/CT findings could also be used in predicting the progression and in guiding the treatment (16, 20, 21). However, a definitive marker or laboratory parameter that can predict the progression has not been determined. In this study, we showed that the values of NLR, PET/CT, SUVmax and DLCO% can be used in order to predict the progression. As a result of one-year follow-up, in the mediastinal lymph nodes, progression at the rate of 60% was observed in cases having the

PET/CT SUVmax value of 14.0 and over, progression at the rate of 80% was observed in cases having the NLR value of 3.20 and over, and progression at the rate of 70% was observed in cases having the DLCO% value of 70.0 and below. In a study previously made, the NLR has been determined higher in stages 2-3 of sarcoidosis cases compared to stage 1. However, this study has not been assessed in terms of progression (22). Similarly, we also determined that the NLR was higher in cases of stages 2,3, and 4 compared to cases of stage 1 ( $p=0.018$ ). In addition, the results of our study reveal that the NLR, which can be calculated in a simple way in the complete blood count, which is a cheap and routine examination, has high sensitivity and specificity in terms of predicting the progression.

## CONCLUSION

In this study, we determined that the values observed in routine hematologic examinations such as NLR, RDW and MPV, were high in sarcoidosis cases. In addition, the values of NLR, DLCO% and PET/CT SUVmax might be used in predicting the progression. At the same, once again we showed that the lung parenchyma involvement in PET/CT correlates with many pulmonary function parameters.

## Authorship and contributorship:

Principal author, Kemal Can Tertemiz, 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.

## REFERENCES

1. Sobic-Saranovic D, Artiko V, Obradovic V. FDG PET imaging in sarcoidosis. *Semin Nucl Med* 2013 Nov; 43(6): 404-11.
2. Cox CE, Davis Allen A, Judson MA. Sarcoidosis. *Med Clin North Am* 2005; 89: 817-28.
3. Hunninghake GW, CostabelU, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of sarcoidosis and other granulomatous disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16: 149-73.
4. McGrath DS, Foley PJ, Petrek M, et al. Ace gene I/D polymorphism and sarcoidosis pulmonary disease severity. *Am J Respir Crit Care Med* 2001 Jul 15; 164(2): 197-201.
5. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *Br Med J* 1961 Nov 4; 2(5261): 1165-72.



6. Jilma B, Blann A, Pernerstorfer T, et al. Regulation of adhesion molecules during human endotoxemia. No acute effects of aspirin. *Am J Respir Crit Care Med* 1999; 159: 857-63.
7. 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.
8. Sarraf KM, Belcher E, Raevsky E, et al. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2009; 137: 425-8.
9. Walsh SR, Cook EJ, Goulder F, et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 2005; 91: 181-4.
10. Tamhane UU, Aneja S, Montgomery D, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol* 2008; 102: 653-7.
11. Gunay E, Sarinç Ulasli S, Akar O, et al. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: A retrospective study. *Inflammation* 2014; 37: 374-80.
12. De Jager CP, Wever PC, Gemen EF, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One* 2012; 7: e46561.
13. Dirican N, Anar C, Kaya S, et al. The clinical significance of hematologic parameters in patients with sarcoidosis. *Clin Respir J* 2016 Jan; 10(1): 32-9.
14. Gibson GJ, Prescott RJ, Muers MF, et al. British Thoracic Society Sarcoidosis study: effects of long term corticosteroid treatment. *Thorax* 1996 Mar; 51(3): 238-47.
15. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force Standardisation of spirometry. *Eur Respir J* 2005 Aug; 26(2): 319-38.
16. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005 Oct; 26(4): 720-35.
17. Mostard RLM, Voo S, van Kroonenburgh MJ, et al. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med* 2011; 105: 1917-24.
18. Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. *Radiographics* 2004; 24: 523-543.
19. Ziegenhagen MW, Rothe ME, Schlaak M, et al. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. *Eur Respir J* 2003; 21: 407-13.
20. Prasse A, Katic C, Germann M, et al. Phenotyping sarcoidosis from a pulmonary perspective. *Am J Respir Crit Care Med* 2008; 177: 330-6.
21. Teirstein AS, Machac J, Almeida O, et al. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest* 2007; 132: 1949-53.
22. Sobic-Saranovic D, Grozdic I, Videnovic-Ivanov J, et al. The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in patients with active chronic sarcoidosis. *J Nucl Med* 2012 Oct; 53(10): 1543-9.
23. Iliaz S, Iliaz R, Ortakoylu G, et al. Value of neutrophil/lymphocyte ratio in the differential diagnosis of sarcoidosis and tuberculosis. *Ann Thorac Med* 2014 Oct; 9(4): 232-5.
24. Oberstein A, von Zitzewitz H, Schweden F, et al. Non invasive evaluation of the inflammatory activity in sarcoidosis with high-resolution computed tomography. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14: 65-72.
25. Rubini G, Cappabianca S, Altini C, et al. Current clinical use of 18FDG-PET/CT in patients with thoracic and systemic sarcoidosis. *Radiol Med* 2014 Jan; 119(1): 64-74.
26. Mostard RL, Verschakelen JA, van Kroonenburgh MJ, et al. Severity of pulmonary involvement and (18)F-FDG PET activity in sarcoidosis. *Respir Med* 2013; 107: 439-47.
27. Cremers JP, Van Kroonenburgh MJ, Mostard RL, et al. Extent of disease activity assessed by 18F-FDG PET/CT in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis* 2014 Apr 18; 31(1): 37-45.