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Role of computed tomography findings, complete blood count parameters and systemic inflammatory markers for predicting the severity in interstitial lung diseases

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Abstract. *Background and Objectives:* The present study aimed to find quantitative and semiquantitative methods to detect the development of fibroproliferative processes at an early stage and predict the severity and prognosis of the disease in interstitial lung diseases (ILDs) using High-Resolution Computed Tomography (HRCT), Pulmonary Function Tests (PFTs) and Complete Blood Count (CBC) parameters. *Materials and methods:* A total of 63 patients (26 female and 37 male) who were admitted to our hospital between January 2014 and January 2018, whose follow-ups were regular and who underwent HRCT, PFT, and CBC examinations on the same day, were included in our study. The median age of the patients included was 65 years (range: 47-79). *Results:* There were significant differences among the mild, moderate, and severe form ILD groups created using the Warrick scoring system for NLR, neutrophil count, and PNR values (p = 0.025, 0.035, 0.006, respectively). Also, there were significant differences among the groups for FVC, FEV1/FVC, PAD, RAA, RV/LV ratio, MLnMD, and MLnC values. Correlation analyses between the parameters revealed significant relationships between Warrick Score, and NLR and neutrophil count, PNR, FVC, FEV1/FVC, PAD, RAA, RV/LV ratio, MLnMD, and MLnC. *Conclusions:* The results of the present study suggested that NLR, neutrophil count, and PNR values could be used as objective evaluation criteria to determine the severity and prognosis in interstitial lung diseases. Also, usage of Warrick Score, FVC, FEV1/FVC, PAD, RAA, RV/LV ratio, MLnMD, and MLnC values could provide quantitative and semiquantitative data for an objective evaluation. Carrying out multicenter studies and creating a scoring system using these parameters could create standardization in determining the prognosis of patients with ILD.

Key words: CT, Fibrosis, Neutrophil-lymphocyte ratio, Platelet-neutrophile ratio, Warrick score

Introduction - aim

Interstitial lung diseases (ILDs) are a large group of diseases that include many different disorders in which radiological, clinical and, pathological findings caused by many known and unknown factors are similar among patients (1). In their pathogenesis, the factors that cause the disease are known to reach alveoli through inhalation and to trigger the damage mechanisms, inducing cytokine release at the tissue level and initiating fibroproliferative processes (2). Also, connective tissue diseases and drugs that cause pulmonary toxicity cause similar effects on tissues (2,3). These processes are generally reversible in the early stages of the disease and respond well to medical and supportive treatment (4). On the other hand, if the diagnosis and treatment are delayed, the prognosis worsens and the disease progresses to

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an irreversible stage (5). Permanent damage to the lungs occurs and could lead to severe respiratory failure (5,6).

In the diagnosis of ILD, detailed anamnesis, smoking, occupational and environmental impact, physical examination findings, routine laboratory tests, pulmonary function tests and, radiological imaging are used (6). In some cases, thoracotomy or thoracoscopic lung biopsies with Bronchoalveolar Lavage (BAL) and Transbronchial biopsy (TBB) are required for patients who cannot be diagnosed or for clinically uncertain diagnoses (6,7). The most important process after diagnosis of ILD patients is to evaluate the response of the disease to treatment and to determine its prognosis (5-7). Accurate evaluation of the response to treatment, accurate determination of clinical course and, the severity of the disease increase the success of medical and supportive treatment (6-8). Pulmonary function tests and radiological imaging methods are frequently used in the determination of prognosis and evaluation of the response to treatment in the follow-up of ILD patients (8-10). On the other hand, the fact that the disease progresses at different rates in each patient and the subjective evaluation of the course of the disease during the follow-ups cause differences in the determination of the treatment response and the prognosis estimation (10-12). The involvement of fibroproliferative processes as a result of elicited tissue-level damage mechanisms in the pathogenesis of interstitial lung diseases has made us think that complete blood count parameters and systemic inflammatory markers could also be used to determine the prognosis of patients. In this context, we aimed to find quantitative and semiquantitative methods that can be used in daily practice in support of computed tomography findings and pulmonary function tests to detect the development of fibroproliferative processes in the early stages and to objectively evaluate the severity and prognosis of the disease.

Material and method

The present study included a total of 63 patients (26 women and 37 men) aged 47 to 79 years who applied to our hospital between January 2014 and January 2018 and had ILD diagnosis, whose HRCT, PFT and, CBC examinations were performed on the same day, who came to their follow-ups regularly, and who had no active infection, history of pulmonary thromboembolism, malignancy, pleural effusion, and lung and mediastinal surgery. The data obtained were evaluated retrospectively. The study has been approved by the local ethics committee (Approval No: 2018/183). All procedures were conducted by the principles of the Declaration of Helsinki.

Multi-Detector CT device in computed tomography unit was used for HRCT imaging (80 row-detector CT 160 slice, Aquilion Prime, Toshiba Medical Systems, Nasu, Japan). The imaging was performed after the patient took the appropriate supine position in the gantry. The scanning began by taking the tomogram images. The tomographic images were then obtained at the end of the inspiration on tomogram at an imaging plane including lung apex at the superior and bilateral costophrenic sinuses at the inferior with a section thickness of 1.25 mm using 120 kVp, 100 mA and, a scanning time of 1 second (13,14). The resulting images were transferred to workstations for processing and evaluation (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA, USA). In all cases, coronal and sagittal reformat images were created in addition to the axial plane.

In HRCT sections obtained based on the specified protocols, images were evaluated in both the mediastinal window (window width: 300 HU, window level: 50 HU) and the parenchyma window (window width: 1400 HU, window level: -600 HU). Warrick scoring system was used for the evaluation of the findings of the lungs in the parenchyma window. In the Warrick scoring system, scoring was made for each patient based on parenchymal lesions and the extent of lesions (15-17) (Table 1) (Fig.1). Those who had scores of 1-8 were classified as mild form, while those with scores of 9-16 were classified as moderate form, and those with 17 and above were classified as severe form (13-18) (Table 2). For the evaluation made in the mediastinal window, on the other hand, main pulmonary artery diameter (PAD), right atrial area (RAA), right ventricular-left ventricular diameter ratio (RV/LV ratio), count of lymph nodes observed in the mediastinum (MLnC)

Table 1. Semi-quantitative scoring method: Warrick et al. (15).

Severity Score		Extent Score	
Ground Glass Opacities	1	1 to 3 segments involved	1
Irregular Pleural Margin	2	4 to 9 segments involved	2
Septal or subpleural lines	3	>9 segments involved	3
Honeycombing	4		
Subpleural cyst	5		
Maximal severity score	**15**	**Maximal extent score**	**15**

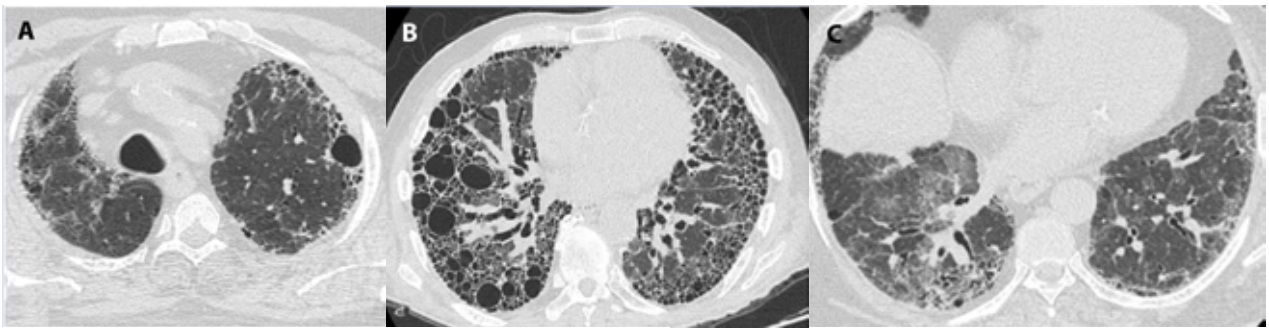

Figure 1. Axial HRCT images of a patient in the severe form ILD group.

Table 2. Demographic distribution within groups.

	Mild*	Moderate**	Severe***	TOTAL
Female	4	14	8	**26 (41,3%)**
Male	4	15	18	**37 (58,7%)**
TOTAL	**8 (12,7%)**	**29 (46%)**	**26 (41,3%)**	**63**

*__Mild form group:__ Warrick Score: 1 to 8
**__Moderate form group:__ Warrick Score: 9 to 16
***__Severe form group:__ Warrick Score: >16

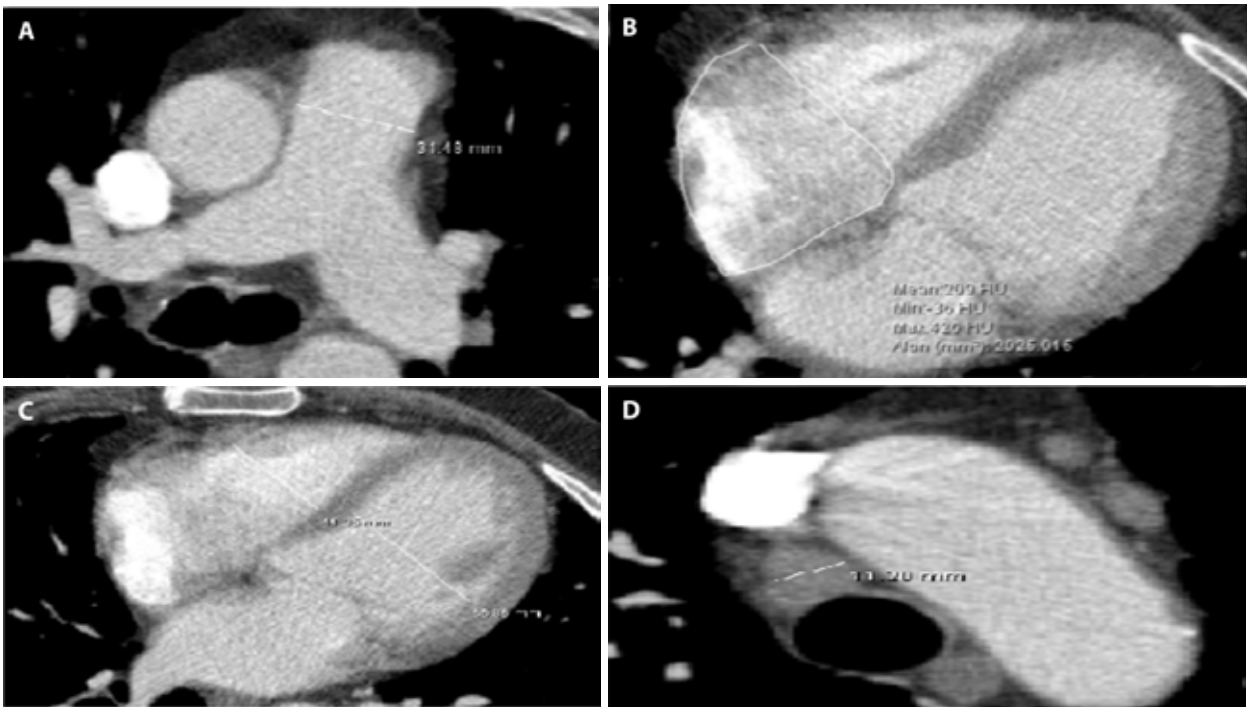

Figure 2. Measurement of the main pulmonary artery diameter (A), right atrial area (B), right ventricular-left ventricular diameter ratio (C) and, short-axis of mediastinal lymph nodes (D).

and mean short-axis diameter of mediastinal lymph nodes (MLnMD) were measured with the help of an electronic ruler in each patient. The main pulmonary artery diameter was measured at 1 cm proximal of the main pulmonary artery bifurcation point, while the right atrial area was measured on the widest transverse plane in the axial CT image (Fig.2). The right ventricular-left ventricular diameter ratio

was determined in the sections that pass through the middle of the ventricles in the axial plane. For each patient, all lymph nodes in the mediastinum were counted, and the mean short-axis diameters of all lymph nodes were measured (19-21). All Warrick scorings and measurements were evaluated by two radiologists. Statistical analyses were performed on the data. Pulmonary function tests of all patients included in the study were performed in the PFT laboratory (nSpire Health GmbH, Germany). In these tests, FEV1, FVC and, FEV1/FVC values of each patient were calculated. Complete blood count parameters of neutrophil, lymphocyte, platelet counts and mean platelet volume (MPV) values which were measured on the same day were used, and the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and platelet-neutrophil ratio (PNR) were calculated for each patient. The data were evaluated using the SPSS 20.0 software (Statistical Package for the Social Sciences, SPSS Inc., Chicago). Pearson correlation test was used to analyze the relationships between the parameters when the data had a normal distribution. Kruskal-Wallis H test was applied to determine whether there was a difference among the mild, moderate, and severe groups created using the Warrick scoring system for the parameters examined. The results were expressed in the 95% confidence range, and p values less than 0.05 were considered statistically significant.

Results

Of the 63 patients in the present study, 37 were male (58.7%) and 26 were female (41.3%). The mean age of the patients was 65 (range: 47-79). Eight of the patients were in the mild group, while 29 were in the moderate group and 26 were in the severe group. Although there was no significant difference in the male/female ratio in the mild and moderate groups, male dominance in the severe group was notable (Table 2). In terms of the diagnoses of the patients followed-up, 30 patients had Idiopathic Pulmonary Fibrosis (IPF), 18 had Nonspecific Interstitial Pneumonia (NSIP) and 15 had Scleroderma (Table 3). The most common diagnosis in the mild group was scleroderma, NSIP was common in the moderate group, and IPF in the severe group (Table 3). There was no significant relationship between the mild, moderate, and severe form ILD groups for age, BMI, BSA, lymphocyte count, platelet count, PLR, and MPV values. However, the differences for neutrophil count, NLR, PNR, PAD, RV/LV Ratio, RAA, MLnC, MLnMD, FVC, and FEV1/FVC values were significant (Table 4). In correlation analysis, Warrick score had a high level of positive correlations with NLR, PAD, RAA, RV/LV Ratio, MLnC, MLnMD, and FEV1/FVC, a moderate level of positive correlation with the neutrophil count, a high level of negative correlation with FVC, and a moderate level of negative correlation with PNR. On the other hand, Warrick's score did not have a significant correlation with the lymphocyte count, platelet count, PLR, and MPV values (Table 5).

NLR values had high level of positive correlations with Warrick Score, PAD, RAA, RV/LV Ratio, MLnMD, and FEV1/FVC, a moderate level of positive correlation with PLR and MLnC, a high level of negative correlation with FVC, and a moderate level of negative correlation with PNR. However, there was no significant correlation between NLR values and MPV (Table 6).

On the other hand, the correlations of the main pulmonary artery diameter with RAA and RV/LV ratio were high and positive (Table 7).

Discussion

In the present study, significant differences were observed among mild, moderate, and severe form ILD groups for NLR, neutrophil count, and PNR values (p: 0.025, p: 0.035, p: 0.006, respectively). Also, Warrick's score had a high positive correlation

Table 3. Diagnosis of followed-up patients and number of patients diagnosed in groups.

	Mild	Moderate	Severe	TOTAL
Idiopathic Pulmonary Fibrosis (IPF)	2	10	18	**30 (47,6%)**
Nonspecific Interstitial Pneumonia (NSIP)	2	11	5	**18 (28,6%)**
Scleroderma	4	8	3	**15 (23,8%)**
TOTAL	**8 (12,7%)**	**29 (46%)**	**26 (41,3%)**	**63**

Table 4. Statistical analysis of age, BMI, BSA, complete blood count parameters, systemic inflammatory markers, cardiac and mediastinal CT findings, and PFT values between the mild, moderate and severe form ILD groups.

	Mild	Moderate	Severe	*p* value
Age (years)	65±11.9* (65.5)**	66.5±11.5 (65)	65.6±10.5 (69)	0.953
BMI (SI)	29.7±5.18 (28.8)	29.2±4.9 (29.1)	26.9±4.6 (26.9)	0.167
BSA (m^2)	1.86±0.15 (1.83)	1.78±0.18 (1.83)	1.76±0.23 (1.74)	0.487
Neutrophil (10^9/L)	2.3±0.86 (1.89)	3.11±1.81 (2.88)	3.72±1.41 (3.24)	**0.035**
Lymphocyte (10^9/L)	2.2±0.69 (2.12)	2.7±3.01 (2.1)	2.19±0.78 (1.95)	0.814
Platelet (10^9/L)	253±66.2 (282)	254.4±53.5 (243)	246.1±79.9 (227)	0.528
NLR	2.2±0.83 (1.86)	3.14±1.85 (2.8)	3.68±1.48 (3.35)	**0.025**
PLR	117,83±23,3 (119)	128,7±67,1 (111,6)	126,5±66,2 (117,8)	0,992
PNR	58.5±19.3 (51.15)	43.6±13.1 (46)	37.3±19.9 (33.75)	**0.006**
MPV (fL)	9.23±1.67 (9.45)	8.78±1.1 (8.9)	9.23±1.27 (9.2)	0.283
PAD (mm)	25.7±2.87 (26)	26.7±2.64 (27)	32.06±2 (31.75)	**0.0001**
RV/LV ratio	<1	<1	>1	**0.0001**
RAA (cm^2)	20.25±3.96 (21.8)	21.42±3.12 (21.1)	30,3±3,02 (29,25)	**0.0001**
MLnC	3,87±0,64 (4)	7,31±1,56 (7)	15,61±1,44 (16)	**0.0001**
MLnMD (mm)	7,06±1,26 (7)	8,6±1,01 (9)	11,64±1,01 (11)	**0.0001**
FVC (L)	2,59±0,54 (2,5)	1,88±0,80 (1,8)	1,43±0,62 (1,45)	**0.001**
FEV1/FVC	83,25±3,41 (82,5)	90,82±6,5 (91)	89,65±6,22 (88)	**0.009**

BMI: Body Mass Index, BSA: Body Surface Area, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, PNR: Platelet-Neutrophil Ratio, MPV: Mean Platelet Volume,
PAD: Pulmonary Artery Diameter, RV: Right Ventricle, LV: Left Ventricle, RAA: Right Atrial Area, MLnC: Mediastinal Lymph nodes Count, MLnMD: Mediastinal Lymph nodes Mean Diameter (Short Axis)
*: mean±SD
**: median value

with NLR values, a moderate positive correlation with neutrophil count and a moderate negative correlation with PNR values. In previous studies, Attila et al. (22) found that NLR values increased in scleroderma patients with lung involvement compared to the patients without lung involvement (p: 0.01). Yang et al. (23) on the other hand, compared the patients with dermatomyositis and healthy controls and observed that NLR values were higher in the patients with lung involvement than the ones without lung involvement and the healthy controls. Similarly, Tezcan et al. (24) compared scleroderma patients with the healthy control group and found that NLR values increased in patients with lung involvement ($p < 0.001$). In their studies dealing with rheumatoid arthritis patients, Chen et al. (25) reported that NLR values were higher in patients with lung involvement compared to the patients without

Table 5. Correlation analysis between Warrick Score and complete blood count parameters, systemic inflammatory markers, cardiac and mediastinal CT findings, and PFT values.

(n=63)	r*	p*
Neutrophil	**0.485**	**0.032**
Lymphocyte	0.085	0.510
Platelet	0.080	0.534
NLR	**0.725**	**0.725**
PLR	0.085	0.510
MPV	-0.080	0.534
PNR	**-0.408**	**0.037**
PAD	**0.728**	**0.009**
RAA	**0.756**	**0.007**
RV/LV Ratio	**0.820**	**0.003**
MLnC	**0.732**	**0.01**
MLnMD	**0.805**	**0.008**
FVC	**-0.803**	**0.006**
FEV1/FVC	**0.826**	**0.005**

Table 6. Correlation analysis between NLR value and Complete Blood Count parameters, systemic inflammatory markers, cardiac and mediastinal CT findings, and PFT values.

(n=63)	r*	*p**
PLR	**0.596**	**0.021**
MPV	-0.043	0.736
PNR	**-0.440**	**0.023**
PAD	**0.718**	**0.009**
RAA	**0.701**	**0.011**
RV/LV Ratio	**0.709**	**0.016**
MLnC	**0.679**	**0.018**
MLnMD	**0.706**	**0.014**
FVC	**-0.702**	**0.008**
FEV1/FVC	**0.711**	**0.006**

Table 7. Correlation analysis between Main Pulmonary Artery Diameter and RAA and RV/LV Ratio.

(n=63)	r*	*p**
RAA	**0.777**	**0.006**
RV/LV Ratio	**0.753**	**0.002**

lung involvement and the healthy control group ($p < 0.001$). Also, Yang et al. (23), Tezcan et al. (24), and Chen et al. (25) found that PLR values increased in patients with lung involvement while Tezcan et al. (24) reported that MPV values decreased in patients with lung involvement. Besides, the patients with lung Involvement were found to have lower lymphocyte count (24,25) and higher platelet values (25). In the present study, we observed that the disease severity was not associated with lymphocyte count, platelet count, PLR, and MPV values. In almost all studies in the literature, patients were grouped as having and not having interstitial involvement in the lungs, and systemic inflammatory markers and complete blood count parameters were compared between these groups. In the present study, on the other hand, patients with lung involvement were grouped as mild, moderate, and severe based on Warrick scoring, and the differences among these groups for the parameters examined were investigated. The fact that the results incompatible with the literature were observed in terms of lymphocyte count, platelet count, PLR, and MPV values in the present study could be attributed to this reason. On the other hand, we suggest that NLR, neutrophil count (26), and PNR values could be used as objective criteria for predicting the prognosis of ILD patients and determining the severity of the disease.

Pulmonary function tests have higher sensitivity than radiological imaging in classifying the severity of interstitial lung disease. However, one of our aims during our study was to group radiological imaging findings and to determine the relationship between pulmonary function tests and to predict the prognostic effect of radiological imaging findings in the follow-up of the disease. In this study, we compared the FVC and FEV1/FVC values between mild, moderate and severe form ILD groups, and there were significant differences between the groups (p: 0.001 and p: 0.009, respectively).The correlation analyses revealed that both Warrick Score and NLR values had high levels of negative correlations with FVC and high levels of positive correlations with FEV1/FVC. In their study evaluating the lung damage in rheumatoid arthritis (RA), Yilmazer et al. (18) compared the data from 70 patients with normal HRCT findings and 60 patients with abnormal HRCT findings. They found that FVC values decreased in the group with abnormal HRCT findings (84.4 ± 20.7) compared to the group with normal HRCT findings (91.8 ± 20.3). However, there was no significant difference between the groups for FVC values (p: 0.094). In their study comparing Warrick scores and pulmonary function tests in patients

with systemic sclerosis, Ibrahim et al.(14) found that Warrick scores were negatively correlated with FVC and FEV1/FVC values. Similarly, there was a high level of negative correlation between Warrick Score and FVC (r: -0.803, p: 0.001) in the present study. On the other hand, unlike Ibrahim et al. (14) there was a positive correlation between Warrick score and FEV1/FVC (r: 0.826, p: 0.001) in our study. In interstitial lung diseases, pulmonary hypertension and cor pulmonale may develop due to respiratory failure in patients with pulmonary fibrosis. Cor pulmonale is a sign of poor prognosis in ILD and indicates advanced-stage disease. In these patients, there may be signs of increased diameter of the main pulmonary artery, pulmonary hypertension, and right cardiac volume overload (27). In the present study, we compared PAD, RAA, and RV/LV ratio values among mild, moderate, and severe form ILD groups, and found significant differences among the groups for all three parameters (p: 0.0001). The correlation analyses showed that both Warrick score and NLR were positively correlated with PAD, RAA, and RV/LV ratio. Also, the correlation analyses between the cardiovascular findings showed high positive correlations of PAD with RAA and RV/LV ratio. In their study dealing with the extrapulmonary findings of systemic sclerosis in HRCT, Farrokh et al. (20) found that lung fibrosis was more severe in systemic sclerosis-related interstitial lung diseases accompanied by pulmonary arterial hypertension (PAH) than in the non-pulmonary arterial hypertension group. By the literature, there was an increase in the main pulmonary artery diameter, right atrial area and right ventricle-left ventricle ratio as the severity of the disease increased in the present study. Indeed, all patients in the severe form ILD group had a main pulmonary artery diameter of 30 mm and above. Also, the RV/LV ratio of the patients in the severe form ILD group was more than 1. Thus, we suggest that PAD, RAA, and RV/LV values can be used as objective evaluation criteria to determine the prognosis of the disease and to identify patients, especially those in the severe form ILD group.

In interstitial lung diseases, mediastinal lymphadenopathy may develop as a result of fibroproliferative inflammatory and infectious processes (1,5,11,19,20). Based on this, we found significant differences among mild, moderate, and severe form ILD groups for MLnMD (mean short-axis diameter of mediastinal lymph nodes) and MLnC values (count of mediastinal lymph nodes) (p: 0.0001). In the correlation analysis, Warrick score and NLR had high positive correlations with MLnMD and MLnC. Especially in the severe form ILD group, the short-axis diameters of the mediastinal lymph nodes were measured to be 10 mm or longer. In the literature, Souza et al. (19) studied mediastinal lymph node growth in 206 patients with idiopathic interstitial pneumonia (IIP), and reported significant increases in the size of mediastinal lymph nodes, especially in cases with severe fibrosis. They found a positive relationship between the severity of the disease and the presence of lymphadenopathy, especially in patients with NSIP ($p = 0.01$). In line with the literature, as the severity of interstitial lung disease increased, there was both growth in mediastinal lymph nodes and an increase in the number of mediastinal lymph nodes in the present study (p: 0.0001). We believe that MLnMD and MLnC values could be used as objective evaluation criteria in distinguishing the particularly severe form ILD patients from mild to moderate-form patients.

Most of the studies in the literature compared lung involvement with one or two groups of parameters. In our study, we compared patients with lung involvement with a total of five different groups of parameters: complete blood count parameters, systemic inflammatory markers, pulmonary function tests, cardiac findings, and mediastinal findings. On the other hand, the important limitations of our study are that it was retrospective, included fewer patients in the mild group than the other groups, lack of echocardiographic findings, lack of histopathological data in some patients and long-term follow-up data. Multicenter studies with a greater number of patients also including patients with other interstitial lung diseases are needed.

In conclusion, we believe that NLR, neutrophil count, and PNR values could be used as objective evaluation criteria to determine the severity in interstitial lung diseases. Also, the use of Warrick Score, FVC, FEV1/FVC, PAD, RAA, RV/LV ratio, MLnMD, and MLnC values would provide quantitative and semiquantitative data that could contribute to objective evaluation. Conducting multicenter studies and establishing a scoring system using the abovementioned parameters could result in standardization in determining the prognosis of patients with ILD.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Informed consent: Informed consent was obtained from all participants of the study.

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