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Parameters effective on survival in connective tissue disease-related interstitial lung disease

Siahmet Atlı[1], Gamze Kırkıl[2], Mutlu Kutluöztürk[2], Önsel Öner[2], Süleyman Serdar Koca[3], Ayşe Murat Aydın[4], Sibel Doğru[5]

[1]*Department of Chest Diseases, Ministry of Health University, Van Training and Research Hospital, Van, Turkiye*
[2]*Department of Chest Diseases, Faculty of Medicine, Fırat University, Elazığ, Turkiye*
[3]*Department of Rheumatology, Faculty of Medicine, Fırat University, Elazığ, Turkiye*
[4]*Department of Chest Diseases, Faculty of Medicine, Fırat University, Elazığ, Turkiye*
[5]*Department of Chest Diseases, Faculty of Medicine, Gaziantep University, Gaziantep, Turkiye*

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ABSTRACT

Aims: Connective tissue diseases (CTD) are systemic diseases that most commonly cause lung involvement. To examine how the disease will progress and survival at the time of diagnosis in connective tissue disease related interstitial lung disease (CTD-related ILD).

Methods: Patients with radiological diagnosis of CTD-related ILD were included in this retrospective study. Seventy-five patients aged over 18 years, who were diagnosed as having ILD radiologically and rheumatoid arthritis, Sjögren's syndrome, polymyositis/dermatomyositis, systemic sclerosis, ankylosing spondylitis, systemic lupus erythematosus. Patients who underwent high-resolution computed tomography, pulmonary function test, carbon monoxide diffusion capacity test, and 6-minute walk test were included in the study. During the 1-year follow-up period, the data of the patients who died and survived were compared.

Results: Of the 75 patients included in the study, 55 were women and 20 were men. There were comorbidities in 56 (74.66%) patients. There was no statistical difference between the patients' CTD subtype and FEV1, FVC, FEV1/FVC, DLCO, 6MWT distance, and 6MWT baseline oxygen saturation. At the end of the 1-year follow-up period, four patients died. Age, sex, smoking, CTD subtype, presence of comorbidities, and chronic obstructive pulmonary disease were not associated with survival, but it was determined that non CTD duration, the presence of CHF, DM, and a fibrosis rate of >10% were statistically significantly associated with survival. Among the serologic markers, ESR (60.25±17.72 vs. 24.52±18.96) and CRP (81.12±80.53 vs. 6.36±7.53) were found to be statistically significantly higher in patients who died; the levels of other markers were similar to patients who survived. FEV1, FVC, and 6MWT distances were significantly lower in patients who died. The presence of emphysema, air cysts, nodule, atelectasis, septal thickening, parenchymal bands, air trapping, honeycomb, opacity, ground-glass, mosaic attenuation, and bronchiectasis was not found to be associated with survival in HRCT. However, calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic change were found to be statistically significantly associated with survival.

Conclusion: We suggest that patients with CTD-related ILD with comorbidity, low baseline respiratory function parameters, a fibrosis rate of >10% on HRCT, calcific nodule, pleural effusion, bronchial wall thickening, and fibrotic changes should be followed more closely in terms of disease progression and mortality.

Keywords: Connective tissue diseases, interstitial lung diseases, survey

INTRODUCTION

Connective tissue diseases (CTD) are systemic diseases that most commonly cause lung involvement. Connective tissue diseases (CTDs) that show features of interstitial lung disease (ILD) include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjögren syndrome (SS), and mixed connective tissue disease (MCTD).[1] The frequency of interstitial lung disease (ILD) in patients with CTD has been reported as 40-50% and is the main cause of mortality and morbidity in these patients.[1] The frequency of lung involvement, clinical findings, prognosis, and response to treatment vary depending on both the histologic subtype and the underlying rheumatic disease. The prevalence of CTD-related ILD varies according to the classification criteria for specific diagnoses and study registries, with higher frequencies in SSc and idiopathic inflammatory myopathies (DM and PM) and lower frequencies in SLE.[1] The presence of ILD in CTD patients has been identified as an important

Corresponding Author: Sibel Doğru, drsibelahmet@hotmail.com

risk factor for poor prognosis. Previous guideline[2] and some studies[3,4] highlight the prognostic relevance of CTD-related ILD with prognosis. However, it is challenging to compare studies and apply study findings to clinical practice because different ILD criteria are utilized in clinical trials. Moreover, due to the complexity of CTD diagnosis, there are insufficient data on parameters that can predict prognosis in patients with CTD-related ILD.

Understanding the factors that may be associated with the prognosis of CTD with ILD may help physicians select more appropriate treatments and improve the prognosis of patients.

This study aimed to investigate clinical-radiologic parameters related to survival in patients with CTD-related ILD.

METHODS

Ethics Approval

Approval was received Fırat University Ethics Committee (Date: 17.10.2019, Decision No: 15/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Seventy-five patients aged over 18 years, who were diagnosed as having ILD radiologically and RA, SS, PM/DM, SSc, AS, SLE in accordance with the guidelines.[1,5-9] Patients with lung malignancy, tuberculosis, chronic obstructive pulmonary disease, and drug or occupation-related ILD were not included in the study.

Study Design

This retrospective study was conducted between 2010-2015. Complete blood counts, blood levels of creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), transaminases, C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) were studied.

Interstitial lung disease was diagnosed through clinical findings, HRCT (Philips Brillance CT 64-slice) and pulmonary function tests (PFT).[1] Patients with septal thickening, air trapping and mosaic appearance, parenchymal bands, subpleural curvilinear lines, bronchial wall thickening, ground-glass appearance, centrilobular opacity, consolidation, honeycomb appearance, nodules, bronchiectasis and emphysematous changes were included in the study. The intensity of fibrosis was recorded on HRCT (lower/higher than 10%).

Pulmonary function tests, carbon monoxide diffusion capacity measurement (DLCO), and the six-minute walk test (6MWT) were performed. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC were evaluated in the respiratory function test. Carbon monoxide diffusion capacity was measured using the single breath method. With the 6MWT, the maximum walking distance of the patient in 6 minutes, who walked at the fastest speed they could along a 55-meter corridor, was evaluated.

The patients received their routine treatments in accordance with the guidelines.[5-9]

At the end of 1 year, the survival status of the patients was recorded.

Statistical Analysis

The results are presented as mean±standard deviation, and the IBM SPSS Statistics 21 statistical program (authorization code: d91314f638c364094170; Armonk, NY, USA) was used to evaluate the data. The Chi-square test was used to compare categorical data, and student's t-test was used to compare paired groups. For all statistical analyses, $p<0.05$ was considered statistically significant.

RESULTS

Seventy-five patients who were diagnosed as having CTD-related ILD were included in the study. Of the patients, 55 (73.3%) were women. The age, sex, and disease duration of the patients according to the subtype of CTD are presented in Table 1. Patients with SLE were significantly younger than patients with RA (p=0.02), patients with RA were significantly older than patients with AS (p<0.001), patients with SS were significantly older than patients with AS (p=0.016), and patients with AS were significantly younger than patients with SSc (p=0.003). There were comorbidities in 56 (74.66%) patients.

There was no statistical difference between the patients' CTD subtype and FEV1, FVC, FEV1/FVC, DLCO, 6MWT distance, and 6MWT baseline oxygen saturation (SpO_2) (p =0.100, p=0.117, p=0.798, p=0.183, p=0.051, and p=0.131, respectively). Only the 6MWT end SpO2 of patients with SLE was significantly lower than that of patients with AS (p=0.021). Pulmonary function test results of the patients are presented in Table 2 (mean±SD).

Table 1. Age and gender distribution of patients according to connective tissue disease subtype

Connective tissue disease subtype	Age	Gender (F/M)	Disease duration (year)
Systemic lupus erythematosus (n=3)	43±19.15	2/1	7.66±2.51
Rheumatoid arthritis (n=29)	59.20±10.05	22/7	7.13±2.21
Sjögren's syndrome (n=3)	59.00±6.08	3/0	10.03±0.11
Ankylosing spondylitis (n=11)	43.45±8.98	2/9	6.63±1.74
Polymyositis/dermatomyositis (n=3)	47.66±15.14	3/0	9.0±1.73
Systemic sclerosis (n=25)	56.64±12.51	22/3	6.92±2.81
Reynaud (n=1)	47	1/0	3

At the end of the 1-year follow-up period, four patients died. The patients who died were observed to be older than surviving patients, although this did not reach statistical significance (63.50±2.64 vs. 54.26±12.57, p=0.083). All patients who died were female, and two were found to have SSc, one had SS, and one had RA.

Age, sex, smoking, CTD subtype, presence of comorbidities, and chronic obstructive pulmonary disease were not associated with survival (p=0.083, p=0.215, p=0.284, p=0.398, and p=0.231, respectively), but it was determined that non CTD duration, the presence of CHF, DM, and a fibrosis rate of >10% were statistically significantly associated with

Table 2. Pulmonary function test, DLCO and 6MWT results according to CTD subtypes

CTD subtype	FEV1 (%)	FVC (%)	FEV1/FVC	DLCO (%)	6MWT (m)	6MWT baseline SpO_2 (%)	6MWT end of SpO_2 (%)
Systemic lupus erythematosus (n=3)	77.33±14.74	77.66±15.01	81.66±4.50	60.50±24.74	283.75±136.11	94.00±4.24	91.50±4.94
Rheumatoid arthritis (n=29)	87.75±18.09	80.42±14.40	83.85±8.85	78.25±30.79	360.68±120.73	95.24±2.06	94.17±2.92
Sjögren's syndrome (n=3)	75.66±12.85	72.00±11.26	79.66±3.51	93.01±32.12	385.00±76.97	94.66±1.15	92.66±2.51
Ankylosing spondylitis (n=11)	89.00±9.41	83.20±10.20	85.10±4.25	81.66±15.19	491.09±94.07	96.45±1.21	96.27±1.84
Polymyositis/ dermatomyositis (n=3)	65.66±3.05	66.66±2.30	79.00±4.35	54.66±19.13	403.33±63.50	96.33±2.08	92.33±7.23
Systemic sclerosis (n=25)	79.29±17.80	73.45±13.64	84.33±7.16	63.21±18.53	356.09±125.76	93.31±4.46	91.22±6.15
Reynaud (n=1)	59	55	87	49	330	96	84

DLCO: Carbon monoxide diffusion capacity, 6MWT: Six-minute walk test, CTD: Connective tissue disease, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, SpO_2: Oxygen saturation

Table 3. PFT, DLCO and 6MWT findings of survival, non survival patients

	FEV1 (%)	FVC (%)	FEV1/FVC	DLCO (%)	6MWT (m) (m)	6MWT baseline SpO_2 (%)	6MWT baseline SpO_2 (%)
Survival (n=71)	84.69±15.25	78.41±12.69	84.36±6.36	71.80±23.23	386.66±119.32	94.91±3.14	93.3 9±4.68
Non survival patients (n=4)	51.50±18.43	54.75±13.12	73.50±13.77	25.26±24.21	221.66±92.24	93.0±1.00	89.33±1.15

PFT: Pulmonary function tests, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, DLCO: Carbon monoxide diffusion capacity, 6MWT: Six-minute walk test

survival (p=0.021, p=0.027, p=0.001, p=0.02, and p=0.017, respectively). Among the serologic markers, ESR (60.25±17.72 vs. 24.52±18.96) and CRP (81.12±80.53 vs. 6.36±7.53) were found to be statistically significantly higher in patients who died (p=0.002 and p=0.001, respectively). As shown in Table 3, FEV1, FVC, and 6MWT distances were significantly lower in patients who died (p<0.001, p=0.001, p=0.054, and p=0.034, respectively). Calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic change in HRCT were revealed to be statistically significant predictors of survival (p=0.019, p=0.001, p=0.016, and p=0.012, respectively).

According to the results of univariate analysis, the effect of statistically significant clinical and radiologic parameters in predicting survival was evaluated using logistic regression (model p=0.001, Cox and Snell R2=0.223). It was found that none of the variables included in the model (FEV1, FVC, FEV1/FVC, 6MWT, DM, CHF, duration of CTD, fibrosis rate >10%, calcific nodule, bronchial wall thickening, presence of fibrotic change) predicted survival (p=0.061, p=0.622, p=0.776, p=0.704, p=0.816, p=0.904, p=0.240, p=0.375, p=0.845, p=0.987, and p=0.295, respectively).

DISCUSSION

We found that, at the end of 1 year of follow-up in patients with CTD-related ILD, it was determined that the presence of DM, CHF, high ESR, CRP, low FEV1, FVC, FEV1/FVC, 6MWT, a fibrosis rate of >10% on HRCT, the presence of calcific nodules and pleural effusion, bronchial wall thickening, and fibrotic changes on HRCT were associated with survival.

It is thought that serologic markers used in the diagnosis and follow-up of CTD may be useful in predicting the development or progression of ILD.[10] In the current study, serum CRP values were significantly higher in patients with fibrosis rates >10% than in those with fibrosis rates <10%, and there was no relationship between other markers (antiCCP, antidsDNA, RF, antiRo, antiScl) and fibrosis rates. Patients with mixed CTD, it was found that the increase in basal anti-RNP antibody titer and the presence of anti-ro-52 antibodies were strong markers predicting the progression of ILD.[10] In recent study, Chiu et al.[4] reported that the positivity of various rheumatologic factors was not associated with poor prognosis. Since the literature is inconsistent, further research should be done on serological markers and prognosis.

It has been reported that the presence of RA-ILD is the second cause of death in patients with RA.[11] The present study, it was observed that patients with RA-ILD were generally aged over 60 years, the majority were women, and 37% were smokers. It has been shown that the risk of developing ILD is high in patients with RA who are aged over 65 years, those with a disease onset age over 65 years, smokers, and those with high anti-CCP titers.[12] In another study, older age, late disease onset, male sex, and high RF levels were found to be risk factors for the development of RA-ILD.[13]

Certain lung function test parameters are frequently used to assess the progression of CTD-related ILD. The current research, it was observed that the basal FEV1, FVC, FEV1/FVC, 6MWT distances of patients who died were significantly lower than those of survivors. Additionally, it was found that the FVC, DLCO, and 6MWT results of those with fibrosis rates >10% were significantly lower than those with fibrosis rates <10%. In a study in which patients with SS-ILD were followed for 15 years, it was stated that a one year decrease in FVC and DLCO values were the best indicators of mortality.[14] In RA-ILD, low DLCO and FVC values measured at the time of diagnosis were associated with the risk of ILD progression.[15] In another study Chiu et al.[4] reported that involving various CTD patient groups, low DLCO level at baseline was associated with poor prognosis in CTD-related ILD patients. Chan et al.[16] reported that significant fibrosis in patients with CTD-related ILD was associated with a rapid decrease in 6MWT distance. According to these results, lung function tests should be performed in patients with CTD-related ILD to evaluate the severity of the disease and to help predict the prognosis.

The importance of evaluating the decrease in PFT parameters in predicting disease progression or mortality is indisputable but because our study coincided with the COVID-19 pandemic period, follow-up measurements of only a small number of patients could be made. Therefore, the interpretation was made based on the basal measurement values.

In the current study, it was determined that the fibrosis rate on HRCT was >10%, and the presence of calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic changes were associated with mortality. In a recent study, it was found that the presence of a usual interstitial pneumonia (UIP) radiologic pattern was associated with the worst prognosis.[17] The UIP pattern has also been found to be associated with both disease progression and mortality in patients with SSc-ILD and PM/DM.[18,19] In a recent retrospective cohort study mortality risk was independently associated with extent of fibrosis on HRCT at baseline (adjusted HR 1.05).[2] Additionally, in another retrospective study, a fibrotic HRCT pattern at baseline was associated with a 3.11-fold higher risk of progression.[20] According to these findings, the presence and severity of fibrosis on HRCT can be utilized to predict prognosis in patients with CTD-related ILD.

Limitations

It was performed in a single center, the number of patients was small, PFT and DLCO measurements could not be performed at certain intervals during the follow-up period, and the number of patients who died was low.

CONCLUSION

Patients with CTD-related ILD with comorbidities, low basal respiratory function parameters, fibrosis rates of >10%, calcific nodules, pleural effusion, bronchial wall thickening, and fibrotic changes should be followed more closely in terms of progression and mortality. Longitudinal studies involving a larger number of patients will contribute to the creation of clinical models that can predict prognosis in CTD-related ILD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Fırat University Ethics Committee (Date: 17.10.2019, Decision No: 15/01).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All authors declare that they participated in the design, execution and analysis of the article and approved the final version.

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