

Prevalence of interstitial lung involvement in patients with connective tissue diseases assessed with high-resolution computed tomography

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Objectives: To assess the prevalence of interstitial lung disease (ILD) in patients with different forms of connective tissue disease (CTD) using non-invasive procedures including high-resolution computed tomography (HRCT) and to evaluate the relationship between the imaging and functional status of the patients.

Methods: Eighty-one subjects with CTD (47 inpatients and 34 outpatients) were evaluated with pulmonary function tests (PFT) and radiological investigations. The extent and severity of lung disease was quantified with an HRCT scoring system previously used in patients with systemic sclerosis (SSc). Interstitial lung involvement was defined as predominantly fibrotic or inflammatory based on HRCT abnormalities.

Results: HRCT abnormalities suggestive of ILD were observed in 69 patients (85.1%), whereas PFT and plain radiograph alterations occurred less frequently (40.7%). The most frequent HRCT abnormalities were septal/subpleural lines and ground-glass appearance whereas lesions consistent with advanced fibrosis were observed in a minority of patients. The HRCT score was higher in patients with abnormal PFT ($p < 0.001$). Thirty-five patients had predominant fibrosis and 34 patients predominantly inflammatory abnormalities. A score of 10 points represented the best compromise between sensitivity and specificity in predicting functional impairment.

Conclusions: A high prevalence of ILD was found based on HRCT abnormalities. However, HRCT scans characterized by minor abnormalities have poor specificity for clinically significant disease and functional findings should also be considered. The large number of patients with predominantly inflammatory HRCT abnormalities suggests that many cases of ILD may be diagnosed in a relatively early stage of the disease.

Interstitial lung disease (ILD) occurs frequently in patients with connective tissue disease (CTD) (1). In systemic sclerosis (SSc), ILD is a common finding and a significant cause of morbidity and mortality (2). Autoptic studies have documented lung involvement in the majority of patients (3, 4). Although several pulmonary disorders have been described in association with rheumatoid arthritis (RA), the most frequent and serious clinical manifestation is ILD (5). Pulmonary abnormalities are often described among the extraglandular systemic manifestations of Sjögren's syndrome (SS), including lymphocytic interstitial pneumonitis and interstitial fibrosis (6–8). In systemic lupus erythematosus (SLE), pleuritis is the most common pulmonary manifestation but evidence of

chronic interstitial pneumonitis has been found in a significant number of patients (9, 10). Interstitial lung disease has also been reported in mixed connective tissue disease (MCTD) (11) and seronegative spondyloarthritis (SA) (12, 13).

The prevalence of pulmonary involvement is heterogeneous in the different forms of CTD. The variability is also accounted for by discrepancies in the methods and diagnostic criteria used in different studies. Although chest X-ray has traditionally represented the first diagnostic step to investigate pulmonary involvement, this method has demonstrated low sensitivity and specificity in ILD, whereas HRCT currently represents the reference technique for a non-invasive approach to lung disease (14). Moreover, HRCT patterns have been shown to correlate with lung biopsy findings and may give prognostic indications (15, 16).

The aim of the present study was to assess the prevalence of ILD in patients with different forms of CTD using a standard protocol of non-invasive

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Table 1. Patient characteristics.

Number of patients	81
Sex, F/M	69/12
Age, years*	57 ± 12.5 (24–79)
Disease duration, years*	10.9 ± 7.9 (1–31)
Diagnosis, n; F/M	
RA	31; 28/3
SLE	17; 16/1
SSc	13; 12/1
SS	8; 8/0
SA	7; 0/7
MCTD	5; 5/0
Smoking status	
Current smokers	16/81
Ex smokers	4/81
Never smokers	61/81
Smoking history, pack years (range)	20.3 ± 7.6 (9–40)
Corticosteroid therapy, n (%)	41 (50.6)
DMARD+corticosteroid therapy, n (%)	32 (39.5)†
Methotrexate	16 (19.7)
Leflunomide	5 (6.1)
Cyclosporin	3 (3.7)
Azathioprine	2 (2.4)
Salazopyrin	2 (2.4)
Hydroxychloroquine	7 (8.6)

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; SA, spondyloarthritis; DMARD, disease-modifying anti-rheumatic drug.

*Mean ± standard deviation (range). Disease duration was calculated from the time of diagnosis to the time of study.

†Twenty-nine patients (35.8%) were receiving one DMARD, three patients (3.7%) two DMARDs.

procedures including HRCT scan and to evaluate the relationship between the imaging and functional status of the patients.

Methods

Eighty-one consecutive Caucasian patients (47 inpatients and 34 outpatients) with a diagnosis of CTD formulated according to the respective current classification criteria (17–22) were included in the study: 31 RA, 17 SLE, 13 SSc, eight SS, seven SA, and five MCTD (Table 1). Hospitalized patients were admitted for: 1) a clinical and therapeutic reevaluation of poorly controlled CTD (16 cases); 2) a planned follow-up assessment (21 cases); and 3) other concurrent medical problems, such as systemic arterial hypertension, secondary diabetes, and renal functional impairment (10 cases). None of the patients was admitted for respiratory reasons.

Pulmonary involvement was investigated initially in relation to clinical data (history, symptoms, and physical examination) and then with pulmonary function tests (PFT) and radiological study. Patients were investigated for the presence of pulmonary symptoms such as dyspnoea, cough, sputum production, wheezing, past medical problems, and risk factors for respiratory diseases

such as smoking, medications, and occupation. Current anti-rheumatic pharmacological treatment was recorded for each patient at the time of the study. Patients with secondary forms of ILD other than CTD were not included in the study. None of the patient presented with history or clinical findings of respiratory infection at the time of the study. Current smokers, ex-smokers (at least one cigarette/day for a minimum of 1 year, cessation at least 3 months before presentation), and non-smokers were identified. Sixteen patients were smokers, four were ex-smokers. There were no significant differences in the prevalence of smokers in each CTD type. In smokers and ex-smokers, cigarette consumption was calculated in pack years (Table 1). Auscultation for thoracic basal crackles was performed.

The patients underwent laboratory evaluation including Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin (Hb), leucocytes (white blood count, WBC), platelets (Plt), rheumatoid factor (RF), anti-nuclear antibodies (ANA) tested with indirect immunofluorescence, and extractable nuclear antigens (ENA) antibodies assessed with an enzyme-linked immunosorbent assay (ELISA). Laboratory data are presented in Table 2.

Pulmonary function tests

Lung function was assessed according to the American Thoracic Society guidelines (23). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were measured with spirometric tests (Sensor Medics, CA, USA); total lung capacity (TLC) was measured with a constant-volume plethysmograph (Sensor Medics); and diffusing capacity of the lung for carbon monoxide (DLCO) was obtained by the single-breath method. The results were expressed as percentage of normal predicted values for age, height, and sex. Pulmonary function was considered abnormal when lung volumes (at least one of: FVC, FEV1, TLC) were <80% and/or DLCO was <75% of predicted values.

Table 2. Laboratory data.

WBC (n/mm ³), mean ± SD	6453 ± 2284
Hb (g/dL), mean ± SD	12.09 ± 1.325
Plt (n/mm ³), mean ± SD	231 468 ± 82 333
ESR (mm/h), mean (range)	30 (4–90)
CRP (mg/L), mean (range)	16.2 (0–208)
RF, n (%)	21 (25.9)
ANA, n (%)	47 (58.02)
ENA, n (%)	29 (35.8)

WBC, white blood count; Hb, haemoglobin; Plt, platelets; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; ANA, anti-nuclear antibodies; ENA, extractable nuclear antigens.

Radiological study

All patients underwent a standard chest X-ray with latest generation digital radiography (Digital Phosphor Storage System, Konica-Minolta) and HRCT scan of the chest (CT Scan Somatom 16; Siemens) the same day that they had functional tests. Scans were performed in the prone position when supine views were suspected of having artefacts due to gravity-dependent perfusion. A high spatial frequency reconstruction algorithm (sharp or bone) was used. HRCT scans were reviewed separately by two radiologists who were blinded to the clinical data.

The parenchymal abnormalities identified on HRCT were coded and a score was defined according to a method used previously in SSc patients (24). Each single segment was evaluated and a point value was assigned to each abnormality (ground-glass appearance, 1; irregular pleural margins, 2; septal/subpleural lines, 3; honeycombing, 4; subpleural cysts, 5). For each patient a 'severity of disease' score was determined by adding point values. An 'extent of disease' score was obtained by counting the number of bronchopulmonary segments involved for each abnormality: 1–3 segments scored 1; 4–9 segments scored 2; >9 segments scored 3. Finally, severity of disease and extent of disease scores were added to form a total HRCT score, with a possible range of 0–30. For example, a patient with a ground-glass appearance (severity of disease score 1) in three segments (extent of disease score 1) and septal/subpleural lines (severity of disease score 3) in five segments (extent of disease score 2) would have a total HRCT score of $1+1+3+2=7$.

A strong correlation between the scores of the two observers was obtained ($y=1.01x+0.07$, $r=0.99$, $p<0.0001$). Interobserver agreement, expressed as κ score after grouping the scores in six classes (0–2, 3–5, 6–8, 9–11, 12–14, >15), was good ($\kappa=0.95$) (25). In 19 cases minor disagreement between the two observers (1 point in 14 cases, 2 points in four cases, 3 points in one case) was resolved with a consensus evaluation.

To estimate the relative proportion of inflammation and fibrosis in each patient, a fibrosis index was assessed that was equal to the number of pulmonary segments demonstrating HRCT

abnormalities suggestive of fibrosis (septal/subpleural lines, honeycombing, and subpleural cysts) divided by the number of segments demonstrating any type of abnormality. On the basis of the fibrosis index, abnormal HRCT scans were defined as predominantly fibrotic (index ≥ 0.5) or predominantly inflammatory (index < 0.5).

Statistical analysis

All statistical analyses were performed with SPSS software version 12.0 (SPSS, Chicago, IL, USA). The Mann–Whitney U-test was used to compare non-parametric data; categorical data were compared with the χ^2 -test. Student's t-test was used to compare normally distributed values. Correlations between two variables were determined with Spearman's r coefficient. The sensitivity and specificity of the HRCT score was evaluated with receiver operator characteristic (ROC) curves.

Results

Thirty-three patients (18 inpatients and 15 outpatients) presented with pulmonary symptoms (exertional dyspnoea and/or non-productive cough). Chest X-ray findings were consistent with ILD in 33 cases (40.7%); a higher prevalence of plain radiograph abnormalities was found in RA patients (17/31, 54.8%).

Abnormal PFT were found in 54 cases (66.6%). In particular, reduced lung volumes were demonstrated in 32 (39.5%) and reduced DLCO in 42 (51.8%) patients. Reduced DLCO without other PFT abnormalities was found in 22 (27.1%) patients. Functional findings in the different diseases are summarized in Table 3.

At least one of the five types of HRCT abnormalities suggestive of ILD was observed in 69 patients (85.1%). The most frequent abnormalities were septal/subpleural lines and ground-glass appearance, demonstrated in 55 (67.9%) and 45 (55.5%) cases, respectively (Table 4; Figure 1). Abnormalities were prevalent in the lower lobes except in SA patients, who mainly presented with HRCT alterations in the

Table 3. Pulmonary function tests in each disease.

	RA	SLE	SSc	SS	MCTD	SA	Total
FVC < 80%	12 (38.7)	4 (23.5)	8 (61.5)	1 (12.5)	0	0	25 (30.8)
FEV1 < 80%	10 (32.2)	4 (23.5)	7 (53.8)	0	1 (20)	0	22 (27.1)
TLC < 80%	9 (29.0)	3 (17.6)	6 (46.1)	2 (25.0)	0	0	20 (24.6)
DLCO < 75%	17 (54.8)	7 (41.1)	10 (76.9)	4 (50.0)	2 (40)	2 (28.5)	42 (51.8)

FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; SA, spondyloarthritis. Values are n (%).

Table 4. HRCT abnormalities in each disease.

	RA	SLE	SSc	SS	MCTD	SA	Total
HRCT abnormalities, n (%)	29 (93.5)	15 (88.2)	10 (76.9)	7 (87.5)	3 (60)	5 (71.4)	69 (85.1)
Ground-glass appearance	18 (58.0)	9 (52.9)	9 (69.2)	3 (37.5)	2 (40.0)	4 (57.1)	45 (55.5)
Irregular pleural margins	17 (54.8)	6 (35.3)	9 (69.2)	5 (62.5)	0	2 (28.5)	39 (48.1)
Septal/subpleural lines	23 (74.2)	12 (70.5)	10 (76.9)	6 (75.0)	1 (20.0)	3 (42.8)	55 (67.9)
Honeycombing	10 (32.2)	5 (29.4)	5 (38.4)	2 (25.0)	1 (20.0)	1 (14.2)	24 (29.6)
Subpleural cysts	1 (3.2)	1 (5.8)	0	0	0	0	2 (2.4)
HRCT scores, mean $\pm$ SD							
Gravity score	5.35 $\pm$ 2.84	4.82 $\pm$ 3.04	5.92 $\pm$ 3.84	4.87 $\pm$ 2.95	1.8 $\pm$ 2.16	3.0 $\pm$ 3.46	4.86 $\pm$ 3.19
Extent score	4.06 $\pm$ 2.14	3.35 $\pm$ 1.99	5.31 $\pm$ 3.49	3.0 $\pm$ 1.7	1.2 $\pm$ 1.3	2.57 $\pm$ 2.50	3.70 $\pm$ 2.49
Total score	9.42 $\pm$ 4.69	8.17 $\pm$ 4.89	11.23 $\pm$ 7.23	7.87 $\pm$ 4.45	3.0 $\pm$ 3.31	5.57 $\pm$ 5.82	8.56 $\pm$ 5.47

HRCT, high-resolution computed tomography; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; SA, spondyloarthritis.



Figure 1. High-resolution computed tomography (HRCT) of a 56-year-old woman with rheumatoid arthritis (RA) and early fibrotic involvement of the lungs. Thickening of interlobular septa in the posterior segment of the left lower lobe has the appearance of septal lines (arrow), that in the right lower lobe depicts a reticular pattern (arrowhead).

upper lobes. Abnormal PFT were found in 52/69 patients (75.3%) with HRCT alterations and 2/12 patients (16.6%) with normal HRCT scan ($p=0.0002$). In particular, 41 (59.4%) patients with HRCT abnormalities presented with decreased DLCO whereas 31 (44.9%) had abnormal lung volumes. The HRCT score correlated with DLCO ($r=-0.76$; $p<0.001$) and TLC ($r=-0.29$; $p<0.001$). Twelve patients (14.8%) presented with abnormal HRCT and no alteration in spirometry, DLCO, or chest X-ray.

The frequency of abnormal HRCT was 33/33 (100%) in patients with symptoms and 36/48 (75%) in patients without symptoms. In patients with pulmonary symptoms the HRCT score was higher (11.39 ± 4.89) than in symptomless patients (6.62 ± 5.02) ($p<0.0001$). No significant difference in terms of HRCT score between the group of smokers (current and ex-smokers) and non-smokers (mean $\pm$ SD: 8.95 ± 5.82 and 8.62 ± 5.06 , respectively) was found. The frequency of abnormal HRCT was equal in smokers and in non-smokers (17/20, 85.0%,

and 52/61, 85.2%, respectively). The HRCT score of patients on methotrexate (MTX) therapy (mean $\pm$ SD: 8.68 ± 5.46) was not significantly different compared to the score of patients not treated with this drug (mean $\pm$ SD: 8.70 ± 5.21).

Two groups were considered based on functional findings: 54 patients (66.6%) with abnormal PFT and 27 patients (33.3%) without functional abnormalities. There were no significant differences between the two groups in terms of age (mean $\pm$ SD: group A 60.44 ± 11.18 , group B 54.04 ± 13.81 years) and disease duration (mean $\pm$ SD: group A 9.63 ± 6.71 , group B 9.42 ± 6.69 years). The scores were higher ($p<0.001$) in patients with abnormal PFT (Table 5).

For each HRCT score we assessed sensitivity and specificity of the abnormal HRCT scans in predicting pulmonary disease with demonstrable functional impairment at PFT. On the basis of the data obtained from the two radiologists, ROC curves were constructed (Figure 2). No relevant difference in the area under the curve was found between the two observers (0.858 for the first radiologist and 0.848 for the second radiologist).

The score of 10 points, as showed by the ROC curves, represented the best compromise between sensitivity and specificity in predicting functional impairment. Sensitivity and specificity associated with this score were 78% and 79% for the first radiologist and 76% and 80% for the second radiologist.

In the 69 patients with HRCT abnormalities, the fibrosis index was 0.49 ± 0.3 . Thirty-five patients had predominant fibrosis (fibrosis index 0.70 ± 0.19) and

Table 5. HRCT scores in patients with and without PFT abnormalities.

	Abnormal PFT	Normal PFT	p-value
Severity score	5.64 $\pm$ 2.88	3.4 $\pm$ 2.92	0.002
Extent score	4.55 $\pm$ 2.12	2.29 $\pm$ 2.12	0.001
Total score	10.2 $\pm$ 4.75	5.7 $\pm$ 4.89	<0.001

HRCT, high-resolution computed tomography; PFT, pulmonary function test.

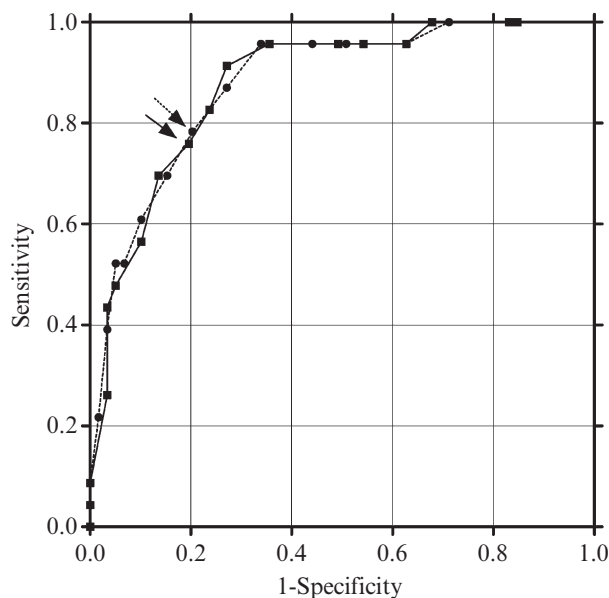


Figure 2. Receiver operator characteristic (ROC) curves demonstrating (arrows) the best compromise between sensitivity and specificity at the high-resolution computed tomography (HRCT) score of 10. First observer: circles and dotted arrow; second observer: squares and solid arrow.

34 patients had predominantly inflammatory (index 0.28 ± 0.24) abnormalities.

In patients with predominantly fibrotic alterations, the total HRCT score was higher (11.57 ± 4.45) than in patients with predominant inflammation (8.50 ± 3.99) ($p=0.003$). No significant differences in functional status, current immunosuppressive treatment, and smoking habit were found between the two groups.

Discussion

In this study HRCT findings in CTD patients were reported according to a nomenclature and scoring system used previously in SSc, which takes into account both the type and the extent of parenchymal abnormalities to obtain a total HRCT score (24). As the type of abnormalities considered is common to several forms of ILD, we tested the performance of this system in a group of patients with different CTD.

In our study HRCT showed abnormalities suggestive of ILD in 85% of the patients. Linear lesions (septal/subpleural lines), which are attributed to thickening of the interstitium by oedema or fibrosis (26), were the most common findings (68%). Ground-glass appearance also occurred in a significant proportion of cases (55%), whereas lesions consistent with advanced fibrosis or end-stage disease, such as honeycombing and subpleural cysts, were observed in a minority of patients. The scoring system we used includes irregular pleural margins among the five types of HRCT abnormalities (24, 27). In fact, irregularities at the parenchyma-pleural interface

have been considered as CT findings consistent with ILD (26, 28). Irregular pleural margins without other abnormalities were found in only two patients in our study and did not contribute to a significant increase in the prevalence of ILD.

Theoretically, non-specific HRCT abnormalities might result in a false increase in the prevalence of ILD. However, in a recent report on 250 volunteers (29), HRCT abnormalities in healthy non-smokers were found only in a minority of cases (about 12%) and possible artefacts could not be excluded because scans were performed only in the supine position.

Chest X-ray abnormalities in RA patients were found in our study more frequently than in previous reports (30, 31). However, some factors limit the comparability between these studies and ours: i) we used latest generation digital radiography, which provides higher spatial and contrast resolution (32); ii) our study included inpatients; and iii) the number of RA cases was significantly different. Although the sampling method differs from other studies in the inclusion of inpatients, it should be noted that none of them was hospitalized for respiratory reasons.

When the relationship between radiological and functional findings was assessed, total HRCT scores was shown to correlate inversely with DLCO and TLC, in keeping with previous reports (27). The score was significantly higher in patients with abnormal PFT than in patients without functional abnormalities. The most sensitive functional test in predicting ILD was DLCO, which was decreased in 59% of patients with HRCT abnormalities. However, 12 patients (15%) had abnormal HRCT findings and no abnormal PFT or chest X-ray, confirming that HRCT may detect earlier signs of ILD.

To evaluate the discriminant capability of HRCT scans in the diagnosis of ILD we have assessed the sensitivity and specificity of each score value in predicting abnormal pulmonary function demonstrable with PFT. On the basis of the data obtained, ROC curves demonstrated that a score of 10 points represented the best compromise between sensitivity and specificity in predicting functional impairment consistent with ILD. These findings suggest that a system of scoring with a wide range of point values (0–30) may be sensitive but not specific in the lowest scores, and minor HRCT abnormalities probably overestimate the prevalence of true ILD. In our study this occurred especially in SLE and SS patients, where the majority of patients had HRCT abnormalities, but these were associated with lower scores and less frequent functional alterations than in SSc or RA. However, score values equal to or greater than 10 predict with acceptable accuracy pulmonary functional impairment and strongly support the diagnosis of ILD.

The scoring system assesses the severity of the disease but does not define with precision the relative extent of inflammation and fibrosis. The differentiation may be helpful in the management of the disease because inflammatory lesions are considered to be more responsive to immunosuppressive treatment than defined and structured fibrosis (33, 34). For this reason we assessed the HRCT fibrosis index. Thirty-five patients presented with predominant fibrosis (index ≥ 0.5) in HRCT scanning and 34 had predominantly inflammatory abnormalities (index < 0.5). Symptoms and PFT abnormalities occurred with similar frequency in the two groups. These findings suggest that the inflammatory stages of the disease, demonstrable by HRCT in an increased number of cases, are not reliably distinguishable from more advanced fibrosis on the basis of clinical and functional data alone.

Despite the potential pulmonary toxicity of MTX, there is no definite evidence of the association between low-dose therapy and chronic ILD (35). In our study patients receiving MTX did not demonstrate higher HRCT scores. Moreover, the number of subjects receiving MTX was similar in patients with predominant fibrosis on HRCT scan and those with predominantly inflammatory abnormalities. The limited number of patients does not allow definitive conclusions but it may be hypothesized that immunosuppressive effects of MTX counterbalance pulmonary toxicity.

The pathogenic role of cigarette smoking in the development of ILD is controversial. It has been reported that smoking is the most consistent independent risk factor predicting the onset of ILD in patients with RA (30). However, this finding was not confirmed in other studies (31). In recent years cigarette smoking has been related to the development of certain forms of ILD, such as desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated ILD (RBILD) (36). In our study the frequency of HRCT abnormalities and the HRCT score were not significantly different between smokers and non-smokers. These findings argue against a major role of smoking in the prevalence of HRCT abnormalities. We cannot exclude the possibility that in some case RBILD/DIP occurred, but the diagnosis needs to be confirmed by lung biopsy (37, 38). Conversely, our patients were investigated with non-invasive methods.

In conclusion, the use of a scoring system allowed us to quantify the extent and severity of lung disease in different forms of CTD. A high prevalence of ILD was found based on HRCT abnormalities. However, our findings suggest that HRCT scans characterized by a low score have poor specificity for clinically significant disease and functional findings should also be considered when minor HRCT abnormalities are observed. Currently, there is no consensus on the

correct timing of therapy in ILD and the development of standardized criteria for staging the disease should be encouraged. The large number of patients with a low fibrosis index and predominantly inflammatory abnormalities suggests that many cases of ILD may be diagnosed in a relatively early stage.

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