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Clinical profile of patients with interstitial lung disease in connective tissue disorders – An original study

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ABSTRACT

Background and Objectives: Interstitial Lung Diseases (ILD's) are a heterogeneous collection of more than one distinct lung disorder which is grouped together owing to their clinical, radiographic, and pathologic features they share in common. Connective tissue disease may be an underlying cause of Interstitial Lung Disease, and often patients may not present with a pre-existing diagnosis. The aim of this study is to study the clinical profile of these patients including physiologic testing and have a better understanding of CTD-ILD in the Indian scenario.

Material and Methods: This was a prospective, observational study conducted at D.Y.Patil Hospital and Medical Research Center, Navi Mumbai, India, between a two year period from December 2017-December 2019. A total of 50 patients of age 18 and above with clinical diagnosis of connective tissue disease and interstitial lung disease were included in the study. Clinical profile of the study participants was studied based on presenting symptomatology and history, chest x-ray and HRCT findings, microbiological aspirates in sputum, pulmonary function testing, 6MWT and 2D-Echo findings. The convenient sampling method was used for data collection and distribution of responses was examined using frequencies and percentages. Further analysis was done using appropriate statistical tests (Chi-square test, t-test) were used to compare responses between various subgroups.

Results: Majority of the study subjects were females (56%) as compared to males (44%). Mean age of the study participants was 58.08 ± 11.92 years, ranging from 27 years to 81 yrs. Majority were of the age group 61-70 years(21%), followed by 51-60 years(16%) respectively. All the participants (100%) presented with dyspnea, more than half of them 28(56%) had cough and over a quarter of them had joint pain 15(30%).17(34%) symptomatic patients of CTD were also diagnosed as ILD. 33(66%) of patients with ILD had underlying CTD.

66% patients of ILD had underlying Connective Tissue Disease. UIP pattern was the predominant in 88% of RA-ILD and NSIP pattern was predominant in other CTD-ILD. Restrictive abnormality on PFT with reduced DLCO was observed in all patients with raised pulmonary artery pressure in 70% patients.

During the 6-minute walk test, 64% of patients walked <350 meters and significantly reduced SpO2 levels were observed after exercise $P<0.05$.

Conclusion: Our study showed a high frequency of lung involvement in the form of respiratory symptoms, radiological patterns, echocardiography, and changes in pulmonary function and exercise testing in patients with ILD diagnosed to have underlying CTD. Since lung involvement in CTD is associated with significant morbidity and mortality, a high index of suspicion in ILD patients with underlying connective tissue disease will help in early diagnosis and treatment of CTD-ILD which is associated with a better prognosis compared to other ILD's. Further studies with a larger sample size and regular patient follow up are required for a better understanding of CTD-ILD in the Indian scenario.

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1. Introduction

ILD refers to a heterogeneous collection of lung disorders that tend to be grouped together since they share clinical, radiographic, and pathologic features. These disorders are sometimes called diffuse parenchymal lung disease (DPLD). Treatments may vary considerably depending on the diagnosis hence a structured approach.

Patients usually present with symptoms cough and dyspnoea on exertion. A detailed history regarding presence of respiratory symptoms with another underlying disease is important. eg. vasculitides, sarcoidosis, amyloidosis, glycogen storage disorders, GERD may all present with persistent cough. History of smoking, environmental exposure and familial disease must be documented.

A careful physical examination usually reveals Velcro crepitation's or crackles. Systemic features of underlying disease may also be present. A review of laboratory data, physiologic studies, radiography, bronchoalveolar lavage and in some cases pathologic tissue obtained from lung biopsy is essential. Multidisciplinary approach is an important part of this process and can have a significant impact on diagnostic and management decisions.[1]

Distinguishing those patients who have a known cause for their ILD (e.g., connective tissue disease, occupational or environmental exposure, or drug toxicity) from those who do not (e.g., IPF, sarcoidosis) is an important step. Connective tissue disease may be an underlying cause of interstitial lung disease, and patients may sometime present with a pre-existing diagnosis. However, most will not and it is important to bring to clinical attention any associated or underlying autoimmune disease as soon as the onset of ILD is diagnosed by the pulmonologist. In some cases, nonspecific symptoms such as night sweats, fever, fatigue, or weight loss may suggest an underlying inflammatory condition. In others, a detailed history and clinical examination of systems aid in the diagnosis of an underlying connective tissue disorder.

For example, careful questioning regarding skin related symptoms may lead to the diagnosis of dermatomyositis as demonstrated by Gottron's papules, a heliotrope rash or "mechanic's hands," all of which may go unnoticed. Patients with underlying systemic sclerosis (scleroderma) may give a history of skin tightness and telangiectasias, raynaud's phenomenon, or digital pitting and skin thickening. Papular eruptions, lupus pernio, and erythema nodosum may be seen in sarcoidosis.[2] Patients with systemic lupus erythematosus (SLE) may present with malar rash, photosensitivity skin reactions, or hair loss.

A detailed review of systems may uncover sequelae of longstanding ILD. In patients with advanced fibrotic lung disease and hypoxemia symptoms like increasing oedema, syncopal events or exertional chest discomfort may indicate core pulmonale and pulmonary hypertension.

The lung is a frequent target of autoimmune-mediated injury in patients with connective tissue disorders due to abundance of connective tissue and blood supply. All compartments of the lung can be potentially affected including airways, lung parenchyma, vasculature and pleura. They can be affected in various combinations and degrees based on the underlying connective tissue disorder and are a significant cause of morbidity and mortality.[3]

There are very few Indian studies assessing the clinical profile of patients with connective tissue disorders in ILD based on physiologic testing. This study aims to assess the clinical profile of patients with connective tissue disorder related ILD based on spirometry, lung volumes, 6MWT, sputum culture and diffusing capacity and help understand the disease better in the Indian scenario.

2. Materials and Methods

This study documents were reviewed and approved by the Institutional Ethics Committee (IEC) of D.Y.Patil Hospital (Navi Mumbai, Maharashtra, India), and was conducted in adherence to good clinical practice (GCP) guidelines and Declaration of Helsinki (DoH).

This was a prospective, observational study conducted between a two-year period from December 2017- December 2019. A total of 50 patients of age 18 and above with clinical diagnosis of connective tissue disease and interstitial lung disease were included in the study from the in-patient as well as outpatient setting. Patients below the age of 18years with only connective tissue disease or only interstitial lung disease were excluded from the study.

After taking written informed consent from each patient, they were provided with a patient information sheet which included personal data, presenting symptoms and past history, HRCT Thorax, PFT, Sputum culture and 2-D Echo findings and performance on 6-minute walk test.

The convenient sampling method was used for data collection and distribution of responses was examined using frequencies and percentages. Further analysis was done using appropriate statistical tests (Chi-square test, t-test) were used to compare responses between various subgroups.

3. Results

Majority of the study subjects were females (56%) as compared to males (44%). Mean age of the study participants was 58.08 ± 11.92 years, ranging from 27 years to 81 yrs. All the participants (100%) presented with breathlessness, more than half of them 28 (56%) had cough and over a quarter of them had joint pain 15 (30%), only 17 (34%) patients had initial involvement of others systems that is 15 (30%) Patients had joint pain and 2 patients (4%) presented with skin tightness. (Table 1)

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Majority were of the age group 61-70 years, followed by 51-60 years respectively. Nearly half of the study participants 21 (42%) had history of hypertension, 13 (26%) had diabetes mellitus. 44 (88%) participants did not have smoking history. 6 (50%) participants who were smokers had 1 pack per year history of smoking.

Majority of the study participants were house wives 22(44%), followed by teachers 8(16%), clerks 7(14%). Number of patients with CTD presenting with symptoms and diagnosed as ILD were 17(34%) and number of patients of ILD diagnosed as CTD (connective tissue disease) were 33(66%) (Table 2). In case of chest x-ray findings, reticular opacities which are predominantly observed seen in lower zones in 47/50 cases (94%). More than two- thirds of the participants showed bilateral lower zone reticular opacities 43(86%) (Table 3).

Among the participants, 17 had RA. Among those patients 15 had UIP pattern and 2 had NSIP pattern on HRCT. Out of 9 patients of systemic sclerosis 4 had UIP pattern and 5 had NSIP pattern. NSIP was predominant in the remainder of CT-ILD participants (Tables 4 and 5). Among the study participants; only 3(6%) patients reported a sputum culture growth. Pseudomonas was cultured in the sputum of patients with polymyositis ILD and two patients with scleroderma ILD had sputum culture positive for staphylococcus.

All the participants showed the restriction pattern on FVC and reduced DLCO. Among the study participants 27 (54%) had mild restriction, 18 (36%) had moderate restriction and 5 patients had severe restriction. All study subjects (100%) had reduced DLCO with a mean of 54.22ml/min/mmHg. The lowest value was 18 ml/min/mmHg in a patient with systemic sclerosis with ILD and highest value of 78ml/min/mmHg in a patient with RA-ILD. 23 (46%) patients had moderately reduced DLCO, 20(40%) patients had mildly reduced DLCO and severely reduced in 7(14%) of patients. However, nearly 43(86%) of the participants showed normal FEV1/FVC ratio. (Tables 6, 7 and 8).

35 (70%) participants showed increased pulmonary artery pressure. Mean pressure of 33.76 with a maximum PASP of 65 and minimum PASP of 18. Among the participants who had pulmonary hypertension (70%), 50% had mild, 14% had moderate and 6% had severe pulmonary hypertension (Table 9). Only 4 (8%) of the participants had mild dilation of the RA/ RV and rest did not show any such findings. Nearly 49 (98%) of the participants had a normal LV Ejection Fraction (LVEF) on 2D echo. The RA/ RV dilation was observed more among the moderate and severely FVC categories when compared to others, this trend was found to be statistically significant (P<0.05). The involvement of RA/ RV dilatation was significantly more among the participants who had severely reduced FEV1 (30-50% of predicted) in restrictive lung disease when compared to another group of mildly reduced FEV1 (50-79% of predicted).

In case of 6-minute walk test; there was a significant difference in pulse rate and SpO2 levels observed between pretest and posttest measurements. Majority of the participants 19 (38%) walked 250- 349 meters on 6 min walk test, followed by 13 (26%) who could only walk 150-249 meters. (Tables 10 and 11)

Table 1: Distribution of subjects based on frequency of symptoms encountered

Symptoms	Number (n=50)	Percent
Breathlessness	50	100
Cough	28	56
Joint pain	15	30
fever	5	10
Tightness of skin	2	4

Table 2: Diagnosis of CT-ILD

Diagnosis of CT ILD	Total	Percentage
CTD diagnosed to have ILD	17	34%
ILD diagnosed to have CTD	33	66%
Total	50	100%

Table 3: Chest X-Ray Findings

Chest X-Ray Findings	Number	Percent
Bilateral lower zone reticular opacities	43	86
Bilateral lower zone opacities with bronchiectasis	2	4
Bilateral lower zone nodular opacities	2	4
Upper zone opacities	3	6
Total	50	100

Table 4: HRCT findings

HRCT findings	Number	Percent
Non-specific interstitial pneumonia	23	46
Usual interstitial pneumonia	27	54
Total	50	100

4. Discussion

As discussed earlier connective tissue diseases encompass a wide range of heterogeneous disorders where lung involvement causes significant morbidity and mortality. Even though the pathogenesis of connective-tissue diseases is unknown, the role of autoimmunity in ILD associated with connective-tissue disorders is well established.[4]

Paolo Spagnolo, Jean-François Cordier, Vincent Cottin[5] concluded that RA affects approximately 1% of the

Table 5: HRCT findings with UIP and NSIP

CT –ILD	UIP	NSIP
RA	15	2
Systemic sclerosis	4	5
Scleroderma	3	4
Sarcoidosis	1	3
SLE	1	2
Polymyositis /DM	1	4
MCTD	2	3
Total	27	23

Table 6: FVC and DLCO

Characteristics	Number	Percent
FVC < 80% (Restriction pattern)	50	100
DLCO < 80 reduced	50	100

Table 7: FVC

FVC (Restriction)	Total	Percentage
Mild	27	54%
Moderate	18	36%
Severe	5	10%
Total	50	100%

Table 8: DLCO grading

DLCO grading	Number	Percentage
Mild (79-60%)	20	40
Moderate (59-40%)	23	46
Severe (<40%)	7	14
Total	50	100

Table 9: PASP grading

PASP grading	Number	Percentage
Mild (26-40)	25	50
Moderate (40-55)	7	14
Severe (>55)	3	6
Total	35	70

Table 10: 6- minute walk test (comparing between pre-test and post-test characters)

Characters	Pre-test (mean)	Post-test (mean)	t- value	Significance
Pulse rate	96.44	121.26	19.451	P <0.005
Spo2	94.84	88.42	8.102	P< 0.005

population worldwide, and women are twice as likely as men to be affected, with the peak incidence being observed between the fourth and sixth decade. Majority in our study were females (56%) as compared to males (44%). Mean age of the study participants was 58.08 ± 11.92 years, ranging from 27 years to 81 yrs. Majority were of the age group 61-70 years (21 patients-42%), followed by 51-60 years (16 patients-32%).

As described by Yang,[6] symptoms considered for diagnosis of ILD-CTDs were dry cough, wheezing, and chest tightness and velcro-like rales that can be heard at the lung bases bilaterally, and clubbing.

Patients may also present with joint pain, dry eyes/mouth dry, Raynaud phenomenon, central muscle weakness, joint swelling deformation, long-term healing of oral ulcers, morning stiffness, repeated unexplained fever, skin

Table 11: Distance walked

Distance walked 6-mwt	Number	Percent
> 350mts	18	36
250- 349mts	19	38
150- 249mts	13	26
Total	50	100

thickening cracking, esophageal reflux.

E. Bodolay, Z. Szekanecz[7] studied ILD with MCTD also described 80% of the study group to have complaints of breathlessness the predominant symptom. ILD is a diffuse parenchymal lung disease, which may be secondary to a variety of occupational or environmental exposures including smoking, and can complicate multiple rheumatic or connective tissue diseases (CTDs) as described by Castelino et al.[8] Majority of the participants in our study were exposed to chulha (biofuel) 18(36%), followed by 11(22%) who gave history of smoking (beedi/cigarette).

In this study rheumatoid arthritis has higher frequency which comprises 34%, 18% had systemic sclerosis, 14% had scleroderma, polymyositis and MCTD constituted 10% each and sarcoidosis and SLE constituted 8% and 6% respectively. Castelino et al.[8] observed frequency of connective tissue disorder associated with ILD was 45% in case of systemic sclerosis and 20-30% with rheumatoid arthritis. In this study rheumatoid arthritis has higher frequency of 34%, followed by 18% in systemic sclerosis, 14% in scleroderma, polymyositis and MCTD constituted 10% each and sarcoidosis and SLE constituted 8% and 6% respectively.

E. Bodolay, Z. Szekanecz [103] describes 96 ILD-CTD patients with chest X-rays showing abnormalities consisting of small irregular opacities predominantly in the bases and middle regions in 87/96 cases (90.6%). In this study 96 out of 144 MCTD patients (66.6%) had active ILD, 75 of this group (78.1%) showed ground glass opacity, 21 patients (21.8%) ground glass opacity with mild fibrosis with HRCT.

E.J Kim et al in their study showed a definite usual interstitial pneumonia pattern in 20 (24%), likely NSIP in 19 (23%) and indeterminate in 43 (52%) out of 82 patients with RA- ILD.[9] In a study of 63 patients with rheumatoid lung disease conducted by David A. Lynch, MB, 26 had a CT pattern suggestive of UIP, 19 had a pattern of NSIP.[10]

Bouros D, Wells AU, Nicholson AG, et al.[11] reported the most frequent histopathologic pattern in systemic sclerosis was NSIP, observed in 62 of 80 patients (77.5%); NSIP was subcategorized as cellular NSIP (15/62, 24%) and fibrotic NSIP (47/62, 76%). Patients with UIP (n = 6) and those with end-stage lung (n = 6) were grouped together, making up 12 of 80 patients (15%).

In our study participants, opacities were predominantly observed in lower zones in (94%), reticular opacities in 86%, nodular opacities in 4% of patients and reticular opacities with bronchiectasis in 4%. 27 (54%) had Usual Interstitial Pneumonia (UIP) and the rest 23 (46%) had non-specific interstitial pneumonia (NSIP). Among 17 patients of RA, 15 had UIP pattern and 2 had NSIP pattern; of the 9 patients of systemic sclerosis 4 had UIP pattern and 5 had NSIP pattern. In the remainder of the CT-ILD participants NSIP pattern was predominant.

Among our study participants whose sputum was tested for culture characteristics, only 3 (6%) showed growth and rest 47(94%) did not show any on culture. Among 3 patients who showed growth in sputum 2 of them had bronchiectatic changes in which 1 patient grew Pseudomonas and another grew Staph Aureus.

Pulmonary function testing of all participants showed a restrictive pattern on FVC and reduced DLCO. 7 (14%) of participants had obstruction on PFT with restriction. Minimum FVC was 42% of predicted and maximum FVC of 78% of predicted. Among our study participants 27 (54%) had mild restriction, 18 (36%) had moderate restriction and 5 patients had severe restriction. All study subjects (100%) had reduced DLCO with a mean of 54.22ml/min/mmHg.

In our study, echocardiography of 35 (70%) participants showed increased pulmonary artery pressure with the rest having normal pressures. Mean pressure of 33.76 with max PASP of 65 and minimum PASP of 18. Among the participants who had pulmonary hypertension (70% of patients) 50% had mild, 14% had moderate and 6% had severe pulmonary hypertension. Among the 35 patients 4 patients had dilated right atrium and right ventricle. Bouros D, Wells AU, Nicholson AG, et al.[11] in their study of systemic sclerosis reported that pulmonary hypertension was evident on echocardiography in 12 of 56 participants (21%); in 44 patients, echocardiographic findings were normal; and in the remaining 18 patients, there was no evidence of pulmonary hypertension.

Chang et al.[12] studied 619 patients of scleroderma with ILD and observed mild to moderate pulmonary hypertension in 154 patients (24.9%), and severe pulmonary hypertension in 77 patients (12.4%). Of the 36.3% with an elevated RVSP measurement, the mean RVSP was 53.3 ± 16.4 mm Hg.

RA/RV dilatation was significantly present among our participants who had severely reduced FEV1 (30-50% of predicted) when compared to another group of mildly reduced FEV1 (50-79% of predicted). The RA/ RV dilation was observed more among the moderate and severely FVC categories when compared to others, this trend was found to be statistically significant.

The six-minute walk test (6MWT) provides powerful prognostic information and has recently been applied to ILD. As compared to resting lung function tests, desaturation to 88% in a baseline 6MWT, either during[13] or at the end of the test,[14]has emerged as a much more powerful predictor of mortality. In a study of patients with

IPF, desaturation to 88% or below was associated with a median survival of 3.21 years compared with a median survival of 6.63 years in those who did not desaturate.[1,5,6] In the present study There was a significant difference observed between pre-test and post-test measurements regarding pulse and Spo2 levels. With mean pulse rate of 96 in pre-test increased to 121 per minute and spo2 level of 94% in pre-test decreased to 88% in post-test.

Among our study subjects 18 (36%) patients were able to walk more than 350 meters, 19 patients were able to cover distance between 250-350 meters and 13 patients covered distance ranging from 150-250 meters.

5. Conclusion

Our study highlights the clinical profile and lung involvement in the form of respiratory symptoms, radiological changes, echocardiography findings, and changes in pulmonary function and exercise testing in CTD-ILD patients. Since lung involvement in CTD is associated with significant morbidity and mortality, a high index of suspicion and the ability to identify the various clinical features and effects on physiological testing in ILD patients with underlying CTD can help in early diagnosis and treatment. One of the drawbacks of this study was the lack of lung biopsy for histopathological confirmation of ILD. Further studies with a larger sample size and regular patient follow up are required for a better understanding of CTD-ILD in the Indian scenario.

6. Sources of Funding

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7. Conflicts of Interest

No conflicts of interest.

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