

Clinicoradiological profile of interstitial lung disease in rheumatoid arthritis



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ABSTRACT

Background: The burden of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients in resource limited countries like India is often under-reported. This study was conducted to find out the clinicoradiological profile of ILD in patients with RA in India.

Aims and Objectives: (1) To find out the frequency of Interstitial Lung Disease (ILD) in Rheumatoid Arthritis (RA) (2) To correlate the clinical findings with those of radiological (Chest x-ray & HRCT Thorax) and pulmonary function tests including Spirometry, TLCO (Diffusing capacity of the Lung for Carbon monoxide/DLCO Corrected for alveolar volume i.e., DLCO/V) Estimation. **Materials and Methods:** Thirty consecutive patients of RA (with or without pulmonary symptoms or signs) who fulfill the American Classification of Rheumatology criteria 1987 were selected from the patients attending the General Medicine OPD (Rheumatology Division) of B.R. Singh Hospital during the study period regardless of being on any medications for RA. This was a cross-sectional, descriptive study. Results were tabulated in Microsoft office excel worksheet and descriptive statistics were expressed as means, standard deviations (SD) mean for continuous normally distributed data and as percentages. Statistical software SPSS version 19.0 was used for data analysis. Unpaired t test (for continuous data)/Chi square test (for proportion) was used for comparing cases and controls. **Results:** The frequency of ILD in RA was 60%. Female patients with a positive rheumatoid factor had a greater chance of development of ILD. The frequency was found to be increased after the age of 40 years. Though in this study 60% of patients had restrictive pattern, 31% had obstructive and 3% had mixed pattern on Spirometry. The patients with deforming RA had greater frequency of restrictive or mixed pattern on Spirometry. 22.22% patients had a decreased TLCO despite having normal CXR. Despite being asymptomatic 12 patients had restrictive lung disease and reduced TLCO with HRCT evidence of ILD. Overall, Spirometry & TLCO are the most appropriate tests to detect restrictive lung disease in patients with RA. In fact, HRCT can show evidence of ILD even when clinical parameters and Chest X-ray are normal. On HRCT of thorax reticular pattern and sub-pleural fibrosis (UIP-Usual interstitial pneumonia) are the predominant pattern. **Conclusion:** The frequency of ILD in RA is quite high. It may be recommended to use Spirometry & TLCO as screening test for detection of restrictive lung disease in patients with RA who should undergo HRCT of chest to confirm presence of ILD in a resource limited setting.

Key words: High-resolution computed tomography; Interstitial lung disease; Rheumatoid arthritis

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INTRODUCTION

Interstitial lung Diseases (ILD)s represent a large number of conditions that involve the parenchyma of the lung—the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between those structures—as well as the perivascular and lymphatic tissues. The disorders in this heterogeneous group are classified together because of similar clinical, roentgenographic, physiologic, or pathologic manifestations.¹

Rheumatoid Arthritis (RA) is only second to systemic sclerosis as far as prevalence of ILD is concerned. Infact, its prevalence has been shown to be greater in smokers.²

Four prospective studies have reported a prevalence of ILD of being between 19% and 44% in the RA population.² The reason for the variability in the prevalence of ILD is the terminology used by different authors. The HRCT appearance in keeping with ILD encompasses a variety of abnormalities including interstitial fibrosis, thickening of non-septal and septal lines, ground glass attenuation, and honeycombing and traction bronchiectasis.^{2,3} Early interstitial lung changes and subclinical alveolitis have been found in up to 40% of RA patients.² The mean age of onset of lung disease is the fifth or sixth decade.²

The etiopathogenesis of RA-ILD is not completely understood although genetic,^{3,4} humoral,⁵ and environmental⁶ factors seem to be involved. The picture is further complicated by the possible ILD-promoting effect of several drugs used to treat RA such as DMARDs (e.g., methotrexate and leflunomide)^{7,8} and biological agents (e.g., anti-TNF alpha and rituximab).^{9,10}

Citrulline is an enzymatically modified post-translationally altered arginine residue that may arise in the course of local inflammation or cellular apoptosis. Anti-CCP antibodies are most commonly found in RF-positive patients, on occasion they can be detected in the absence of RF. In early RA, the assessment of anti-CCP may be the most useful to confirm the diagnosis and establish a likely prognosis. The presence of anti-CCP is most common in persons with aggressive disease, with tendency for developing bone erosions. The development of anti-CCP is most frequent in individuals with an RA associated HLA-β1 allele and in those who smoke cigarettes.¹¹ Intra- and inter-molecular epitope spreading of antibodies targeting self-proteins is well described in several autoimmune disorders, including RA. In particular, epitope spreading of autoantibodies targeting citrullinated proteins was found to precede RA diagnosis by several years, and the accumulation of greater numbers of specific anticitrullinated protein antibodies (ACPA) was associated with higher levels of multiple systemic inflammatory cytokines.¹² However,

neither specific ACPA nor epitope spreading, in general, has been described with ILD in RA estimate prognosis.^{12,13}

The prevalence of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients in resource limited countries is often under-reported largely due to the absence of availability and affordability of High Resolution Computed Tomography (HRCT) scans.

With this idea in mind, we undertook the study of clinicoradiological profile of ILD in patients with RA in our country.

AIMS AND OBJECTIVE

(1) To find out the frequency of Interstitial Lung Disease (ILD) in Rheumatoid Arthritis (RA) (2) To correlate the clinical findings with those of radiological (Chest x-ray & HRCT Thorax) and pulmonary function tests including Spirometry, TLCO (Diffusing capacity of the Lung for Carbon monoxide/DLCO Corrected for alveolar volume i.e., DLCO/V) Estimation.

MATERIALS AND METHODS

The cross-sectional, descriptive study was conducted for a period of 2 years from 01.08.2008 to 31.07.2010 in the Rheumatology outpatient department (OPD) of B.R. Singh Hospital, Kolkata, India which is a tertiary care hospital serving wide range of Indian railway employee and their dependent population. Thirty consecutive patients of RA, regardless of being on any medications for RA with or without pulmonary symptoms or signs who fulfill the American Classification of Rheumatology (ACR) criteria 1987, were selected from the patients attending the rheumatology clinic of the hospital during the study period. Purposive sampling procedure was used to select participants. Detailed assessment of RA (Number of swollen joints out of the 28 joints, Number of tender joints, out of the 28 joints, Visual Analogue scoring, Rheumatoid factor and radiography of hand, Erythrocyte sedimentation rate), assessment of ILD (History, clinical examinations, Chest X-ray PA view, Spirometry, TLCO estimation, HRCT of chest) were done in all patients. The patients meeting the exclusion criteria (Overlap syndromes, already diagnosed obstructive lung disease, other co morbidities like hypertension, diabetes, etc) based on history, examination and investigations were excluded from the study.

Spirometry was performed according to American Thoracic Society guidelines. DLCO corrected for alveolar volume (DLCO/V=TLCO) were measured. Measurements were obtained without bronchodilator administration.

Contiguous scans were obtained with 7-mm or 10-mm collimation CT through the chest. Thin-section CT images were reconstructed with a high-spatial-frequency algorithm. CT scans were obtained at suspended end-inspiratory effort with the patients in the supine position and without intravenous contrast material.

The ethical clearance was taken from Institutional Ethical Review committee and written informed consent was taken from all the participants separately.

Results were tabulated in Microsoft office excel worksheet and descriptive statistics were expressed as means, standard deviations (SD) mean for continuous normally distributed data and as percentages. Statistical software SPSS version 19.0 was used for data analysis. Unpaired t test (for continuous data)/Chi square test (for proportion) was used for comparing cases and controls.

RESULTS

The frequency of ILD in RA was 60%. The gender, rheumatoid factor positivity was not predictive of the presence of ILD. This study found female patients with a positive rheumatoid factor had a greater frequency of developing ILD (Table 1).

Despite being asymptomatic 12 patients had restrictive lung disease and reduced TLCO with HRCT evidence of ILD. Six (33.33%) patients had symptoms of ILD. Only one (16.67%) symptomatic patient had normal CXR despite having ILD. 22.22% patients had a decreased TLCO despite having normal CXR.

In this study it is found that 60% of patients had restrictive, 31% obstructive while 3 % had mixed pattern on Spirometry (Figure 1). Spirometric evidence of lung involvement was present in eighteen out of thirty patients. Only fourteen of them had abnormalities detectable on chest radiograph (46.67%) including bilateral reticular infiltrates (Table 1).

When different spirometric pattern were compared in deforming vs. non deforming RA patients it was observed that patients with deforming RA had greater frequency of restrictive or mixed pattern while amongst the patients with non-deforming disease (no=9) 60% had restrictive, 0 % mixed, 0 % obstructive and 0 % normal(Figure 2).

In this study subpleural fibrosis and reticulonodular pattern were found to be the predominant HRCT findings. Among patients with ILD 77.78% patients had bibasal sub pleural fibrosis and reticulonodular pattern whereas 27.78% Ground glass opacities and 11.11% honeycombing and 5.56% pleural effusion

5.56% had Pleural effusion in HRCT of chest (Figure 3). In our study prevalence of ILD in RA was calculated by chest X-ray and compared with spirometry and found that 22.22% patients had a decreased TLCO despite having normal Chest X-ray.

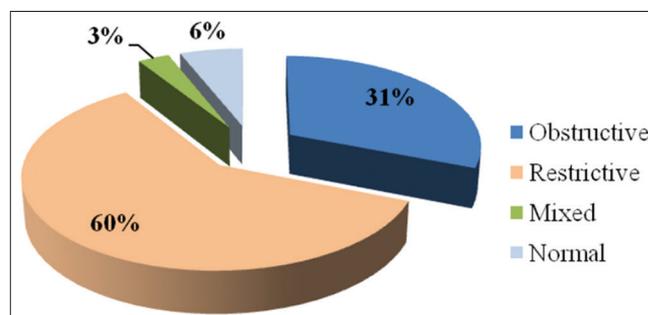


Figure 1: Pie chart showing different lung involvement pattern on PFT

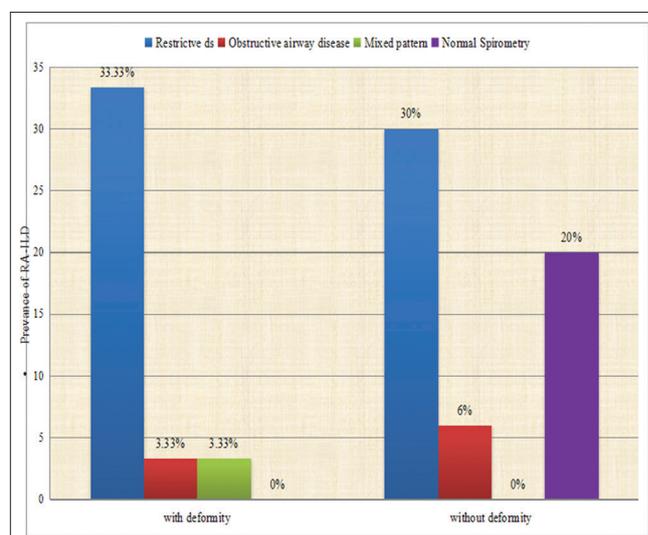


Figure 2: Bar diagram showing comparison between deforming and non-deforming RA on different spirometric pattern

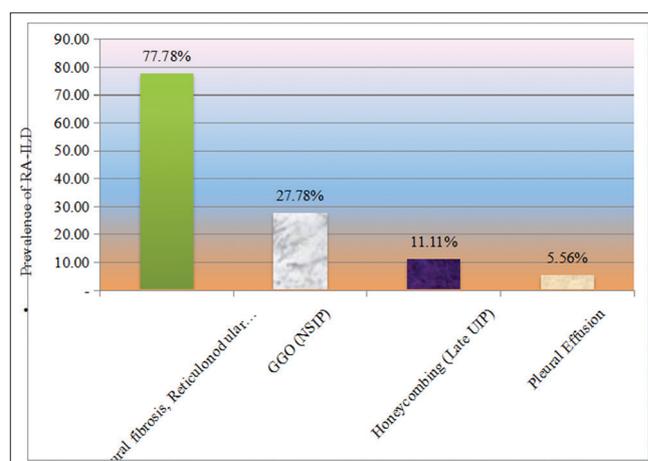


Figure 3: Bar diagram showing different HRCT patterns in patients of RA with ILD

Table 1: Characteristics of cases (n=18; RA with ILD) vs controls (n=12; RA without ILD)

Characteristics	RA-ILD patients N=18(%)	RA without ILD patients N=12(%)	p-value
Sex(M:F)	2:16	2:10	0.661
Rheumatoid factor(+)	66.67	58.33	0.643
CXR Abnormalities	46.67	8.33	0.002
Spirometry (Restrictive)	100 (rest.)	50 (25 rest. 25 obst.)	0.001
Transfer factor(Decreased)	100	25	<0.001
HRCT Abnormalities	100	25	0.001

HRCT was abnormal in eighteen patients (60%) and hence more sensitive than chest radiograph to detect pleuropulmonary involvement in patients of RA. Three patients had abnormalities other than ILD in HRCT.

DISCUSSION

The frequency of pulmonary abnormalities found in association with RA has been shown to vary widely and is likely to depend on multiple factors such as the stage in the disease patients are studied, the source of patient referral and the parameters used to define the disease.

Our study differs from others in that we have reviewed a group of patients who are heterogeneous with respect to the duration (of RA) which varies from months to years. Therefore this study involves patients with both early and long standing disease.

Secondly, our study specifically includes patients with confirmed RA as defined by ACR criteria who were studied irrespective of the presence of respiratory symptoms. These patients were referred mainly from other primary or secondary care hospitals and therefore are more likely to reflect the spectrum of rheumatoid disease in a tertiary hospital cohort.

Finally, we have used a comprehensive group of investigations sensitive for the detection of early disease to detect abnormalities.

The prevalence of ILD in our cohort of RA patients was 60% that is greater than most studies. Such a high prevalence may be attributed to the fact that our patients were selected from a referral specialty clinic. It is therefore difficult to compare the observed prevalence of clinically significant ILD in our study with that of others. Most studies however, have reported the prevalence of significant ILD as ranging from 2.5% to 41%.⁸

In contrary to most other studies where a male predominance^{14,20} has been reported, the presence of ILD was unrelated to the gender of the patient in this study. This too may be attributed to the fact that the patients were

selected from a referral specialty clinic and therefore does not represent the population at large.

No statistical significance found with visual analogue scale, ESR level with prevalence of RA-ILD but it can be due to the fact, that these patients in this study were selected irrespective of their medication status which can bring down the disease activity level and clinical improvement in VAS score.

Unlike other studies,²⁰ we found a strong association of the presence of ILD with the presence of articular deforming disease. This is probably related to the fact that patients came to the health facilities later after developing deformities when they became attentive and conscious about their disease.

In this study we found that patients with high seropositivity with higher anti CCP antibody levels had a greater prevalence of ILD. This is comparable to most other studies that too have reported such an association.^{20,22}

As expected, we found Chest X-Ray to be inadequate to diagnose ILD especially when the disease is in its very early stages. In fact, 30% of our ILD patients had decreased DLCO despite having a normal Chest X-Ray. Notably, this included one symptomatic patient and three asymptomatic patients. However, spirometry was abnormal in all these patients indicating the need to screen RA patients for ILD with spirometry irrespective of the presence of symptoms or Chest X-ray abnormalities. Although HRCT is held to be the gold standard for diagnosing interstitial lung disease, this being an expensive tool may not be a feasible option for all. Spirometry on the other hand is cheap, readily available and can be easily done even during clinic visits.

The HRCT pattern in this study was similar to other studies; reticular pattern and subpleural fibrosis being the predominant patterns (i.e., UIP).¹⁴⁻²¹

However, contrary to Remy-Jardin's retrospective study¹⁴ we did not find a high prevalence of bronchial abnormalities in HRCT.

The HRCT pattern in this study was similar to other studies; reticular pattern and subpleural fibrosis being

the predominant patterns (i.e., UIP: Usual interstitial pneumonia).²³⁻²⁸ However, contrary to Remy-Jardin's retrospective study¹⁴ we did not find a high prevalence of bronchial abnormalities in HRCT.

Limitations of this study

1. As it is a cross-sectional study, therefore, causal relationships cannot be established for which longitudinal study and long-term follow up is needed.
2. The patient population being selected from a referral specialty clinic may not be representative of the entire population.
3. Patients were included irrespective of the nature of medications being used to treat RA; it being known that methotrexate may cause interstitial lung disease.

CONCLUSION

The interstitial lung disease affects a large number of the patients affected with RA. Overall, HRCT or spirometry is the most sensitive tests to detect early interstitial changes in patients with RA. Therefore, it may be recommended to use spirometry as a screening test prior to ordering a HRCT scan whenever ILD is suspected in RA patients. Screening should be considered in patients with longer duration, deforming disease, those with a high anti CCP titers and female RA factor positive patients even if asymptomatic.

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Authors Contribution:

PB and KG- Conceptualized study, literature search, statistically analyzed and interpreted, prepared first draft of manuscript and critical revision of the manuscript; **SG and BG-** Concept and design of the study, reviewed the literature, manuscript preparation and critical revision of the manuscript; **SS and AD-** Concept of study, collected data and review of study.

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