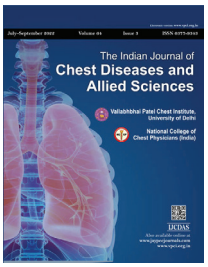
ORIGINAL ARTICLE

Study of Pulmonary Function and Chest Radiographic Abnormalities in Patients with Rheumatoid Arthritis



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CVS Manasa[1], Chandra Sekhar Konda[2], B Siddhartha Kumar[3], KM Bhargav[4], Alladi Mohan[5], R Suryudu[6], Sirisha Kommireddy[7], B Vijaya Lakshmi Devi[8]

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Abstract

Background: Interstitial lung disease (ILD) is one of the important contributors for morbidity and mortality in rheumatoid arthritis (RA) patients. There is paucity of reliable published data on burden of lung disease in RA patients from Andhra Pradesh, India.

Materials and methods: This was an observational study in which 88 patients were evaluated. History and clinical features, including disease-severity score, imaging, and pulmonary function tests were recorded. The data were subjected to statistical analysis.

Results: The mean age was 49.4 ± 10.3 years. Females outnumbered males. Disease duration was less than 2 years in 60.2% of subjects. Respiratory complaints were noted in 12 patients. Seropositivity was noted in 59% of patients. Based on Disease Activity Score 28, high disease activity was seen in 70.5%, moderate activity in 25%, remission in 3.4%, and low activity in 1.1%. Chest radiography showed abnormalities in 4.5%. Pulmonary function tests revealed abnormalities in 23.9% of patients. High disease activity, duration of disease, and seropositivity were not significantly associated with respiratory abnormalities in our study.

Conclusion: Patients with RA should be evaluated for pulmonary involvement during their routine follow-up, which can be helpful in early detection and intervention of ILD and therefore reducing morbidity and mortality.

Keywords: Chest radiography, Disease activity score 28, Interstitial lung disease, Pulmonary function tests, Rheumatoid arthritis.

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Abbreviations used in this Article

ILD = Interstitial lung disease; RA = Rheumatoid arthritis; RA-ILD = Rheumatoid arthritis-associated interstitial lung disease; RF = Rheumatoid factor; Anti-CCP = Anti-cyclic citrullinated peptide; PFT = Pulmonary function tests; CRP = C-reactive protein; Hb = Hemoglobin; ESR = Erythrocyte sedimentation rate; DAS28 Score = Disease Activity Score 28; CXR = Chest X-ray; IQR = Interquartile range; FEV = Forced expiratory volume; FVC = Forced vital capacity

Introduction

Rheumatoid arthritis is a chronic autoimmune systemic inflammatory disease that primarily affects small joints of the hands and feet in a symmetrical pattern. The global prevalence of RA has been estimated as 0.24% based on the Global Burden of Disease 2010 Study.[1] Rheumatoid arthritis affects about 0.75% of adult population in India.[2] Among the various extra-articular manifestations of RA, lung disease is one of the major contributors to morbidity and mortality and is the second most common cause of death after cardiovascular disease.[3] Though pleuritis is the most common pulmonary manifestation of RA lung, it is often asymptomatic and found only in the autopsy, making ILD the most common presenting illness.[4] Other manifestations include pleural effusions, rheumatoid pulmonary nodules, and airway diseases like bronchiolitis and bronchiectasis. Clinically significant rheumatoid arthritis-associated interstitial lung disease (RA-ILD) occurs in about 10% of the population.[4] Male sex, older age, cigarette smoking, presence of high-titer rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP), and gain-of-function MUC5B (mucin 5B) promoter variant are important risk factors for RA-ILD.[5] Less is known about the relation of disease activity with pulmonary manifestations in RA.

Screening of all RA patients for pulmonary involvement has been recommended by some experts[6] considering the toll of morbidity and mortality caused by lung disease. Early detection of pulmonary involvement leads to timely treatment, resulting in the reduction of morbidity and mortality. Although the HRCT chest radiography is the most sensitive method for detecting ILD, its use for screening of asymptomatic individuals is limited in countries like India because of its high cost in addition to high radiation exposure. In such situations, alternative diagnostic modalities

[1–6]Department of Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

[7]Department of Rheumatology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

[8]Department of Radiodiagnosis, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

Corresponding Author: Sirisha Kommireddy, Department of Rheumatology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India, Phone: +91 9490038700, e-mail: sirishakommireddy08@gmail.com

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like pulmonary function tests (PFT) can be considered as low-risk and low-cost diagnostic modalities for early detection of lung disease in RA. The data on the incidence of PFT abnormalities in RA patients are widely varied. Sparse published data are available regarding the pulmonary involvement in RA patients from the state of Andhra Pradesh. Hence, the present study is designed to estimate the burden of lung disease as evaluated by pulmonary function tests and chest radiography in RA patients with varying disease severity.

Materials and Methods

Consecutive adult patients aged 18 years or more diagnosed with RA as per American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria[7] attending Medical and Rheumatology services at the Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, a tertiary care teaching hospital during the period March 2019–March 2020, were included in this study. Age below 18 years, past history of pulmonary tuberculosis, recent lower respiratory-tract infection, pre-existing cardiac disease, and unwillingness to participate in the study were the exclusion criteria. The study was approved by Institutional Ethics Committee. A written informed consent form was obtained from all study participants.

Study Procedure

A detailed history regarding the presence of respiratory symptoms, occupational exposure, and smoking was taken. Dyspnea was quantified based on the Modified Medical Research Council dyspnea scale.[8] Demographic and clinical data were collected with precision. Patients were classified into two categories based on the duration of disease. Patients with disease duration less than or equal to 2 years were considered under early RA, and those with duration more than 2 years were classified under late RA. A general physical and respiratory examination was done in all patients. Arterial oxygen saturation of patients with room air (SpO_2) was obtained using a pulse oximeter (model SS 01, Dr Trust, India) at rest. Based on the SpO_2 values, patients were classified as "normal oxygenation" (SpO_2 ≥95%), "mild hypoxemia" (SpO_2 at 88–94%), or "severe hypoxemia" (SpO_2 <88%).[9] Information on RF, anti-CCP, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), as well as on the current and previous usage of disease-modifying antirheumatic drugs and anti-inflammatory drugs, was collected from the patient charts. Patients with either RF or anti-CCP or both positive were considered as having seropositive RA. Disease-activity severity was assessed by Disease Activity Score in 28 joints[10] (DAS28 score). A patient with a DAS28 score of less than 2.6 was in remission, a score greater than or equal to 2.6 and less than 3.1 indicates low activity, a score greater than or equal to 3.1 and <5.1 indicates moderate activity, and a score of 5.1 or more indicates high activity.

Chest X-rays (CXRs) were obtained with a digital radiography system SEDECAL PRORAD 3N in postero-anterior view, at maximum inspiration. The CXR images were analyzed by a radiologist and were assessed for the presence of lung abnormalities. In all of the patients, pulmonary function testing was done using EasyOne Pro™ (ndd Medical Technologies, Andover, MA, USA), and the results and severity of PFT abnormalities were interpreted as per the American Thoracic Society/European Respiratory Society guidelines.[11–13] The reduction in the mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$) less than the lower limit of normal was considered as a small-airway disease.[13]

Statistical Analysis

Data were recorded on a predesigned proforma and managed using Microsoft Excel worksheet (Microsoft Corp., Redmond, WA). All the entries were double-checked for any possible error. Descriptive statistics for categorical variables was performed by computing the frequencies (percentages) in each category. For the quantitative variables, the approximate normality of distribution was assessed. Variables following normal distribution were summarized by mean ± standard deviation, the remaining variables were summarized as median [interquartile range (IQR)]. Categorical variables were reported as percentages. Continuous variables were compared using Student's *t*-test, Mann–Whitney *U*-test; categorical variables were compared using Chi-square test or Fischer's exact test as appropriate. All *p* values were two-tailed, *p*-value <0.05 was considered statistically significant.

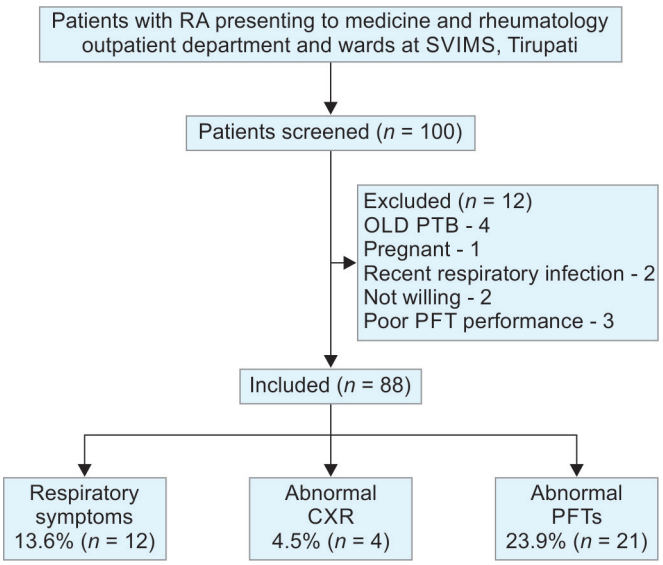
The statistical software IBM SPSS Statistics Version 22 (IBM Corp. Somers NY, USA) was used for statistical analysis.

Results

A total of 100 patients were screened and considered for inclusion in the study. Twelve patients were excluded from the study, reasons being pregnancy (*n* = 1), old pulmonary tuberculosis (*n* = 4), recent respiratory tract infection (*n* = 2), not giving consent (*n* = 2), and poor PFT performance (*n* = 3). The remaining 88 patients satisfying inclusion criteria were considered for analysis (Flowchart 1).

The mean age of study subjects was 49.4 ± 10.3 years. There was female predominance (*n* = 80). The majority of patients belong to the class of early RA (60.2%). Dyspnea (13.6%), dry cough (2.2%), and wheeze (1.1%) were the chief respiratory symptoms noted in patients. Only one person (1.1%) was a former smoker, and the rest of them were nonsmokers. Out of the 88 patients included in the study, 20 were already using drugs for RA, of which 5% of patients were on steroids alone, 11% of patients were using steroids and methotrexate, and 7% of patients were on steroids, methotrexate, and leflunomide at the time of evaluation. On clinical examination, bilateral basal crepitations were noted in 7 patients, and mild hypoxemia was noted in 1 patient. The minimum ESR was

Flowchart 1: Study plan



CXR, chest X-ray; PFT, pulmonary function test; PTB, pulmonary tuberculosis; RA, rheumatoid arthritis

8 mm/hour and the maximum was 120 mm/hour with a median of 48 mm/hour (IQR = 48.25 mm/hour). Seropositivity was noted in 59% of patients. Rheumatoid arthritis was positive in 42% of patients. Anti-CCP was positive in 49% of patients. Both RF and anti-CCP positivity were seen in 31.8% of patients.

As per DAS28 scoring system, majority of the patients (70.5%) had high disease activity and 25% had moderate disease activity. Three patients were in remission, and one had low disease activity. Chest radiographs in most of the patients (95.5%) revealed a normal study. Pleural effusion (unilateral right-sided) was evident in two patients, bilateral bronchiectasis and bilateral lower-zone reticular thickening one in each. Of the four patients with abnormal CXR, two patients had moderate disease activity and the remaining two patients had severe disease activity. CXR was normal in patients with remission and low disease activity. About 96.7% of patients with high disease activity and 91% of patients with moderate activity had normal CXR (Table 1).

Pulmonary function tests were normal in 67 subjects, a restrictive pattern was observed in 20 subjects, and the obstructive pattern was noted in one patient. Mean forced expiratory volume in the first second (FEV_1) was 1.57 ± 0.42 liters, mean forced vital capacity (FVC) was 1.88 ± 0.46 liters, and mean $FEF_{25–75\%}$ was 2.03 ± 0.86 liters/second. Among the patients with abnormal findings on PFT (n = 21), 38% of patients had moderate restriction, 33% had moderately severe restriction, and 19% had mild restriction. Severe obstruction was noted in 4.7% and severe restriction in 4.7% (Fig. 1). Out of 88 patients included in this study, 29 had decreased $FEF_{25–75\%}$ than the lower limit of normal. It was also observed that in subjects with normal PFT patterns (n = 67), 14 patients had decreased $FEF_{25–75\%}$.

All the patients who were in remission (n = 3) had normal spirometry. About 34.8% of patients with low–moderate activity had a restrictive pattern, 19.3% of patients with severe activity had a restrictive pattern, while the obstructive pattern was evident in one patient (Table 2). In the present study, no statistically significant difference was found between high DAS28 scores and PFT abnormalities (p = 0.32) (χ^2 = 0.968).

Pulmonary function tests were abnormal in 22.6% of patients with a normal CXR (restrictive defect in 18, obstructive defect in 1). Half of the patients with abnormal CXR had a restrictive defect on PFT.

Respiratory abnormalities in the form of symptoms or PFT or chest radiograph changes were seen in 24.5% of patients with disease duration less than 2 years and 40% of patients with disease duration of more than 2 years (Table 3). No statistically significant difference was found between the duration of disease and abnormal findings (p = 0.12) (χ^2 = 2.37). In the present study, seropositivity was also not found to be significantly associated with respiratory abnormalities (p = 0.98) (χ^2 = 0.0005).

Table 1: Chest X-ray abnormalities with disease severity in patients with RA

	Remission	*Low activity*	*Moderate activity*	*Severe activity*
Normal CXR	3	1	20	60
Abnormal CXR	0	0	2	2

CXR, chest X-ray; RA, rheumatoid arthritis

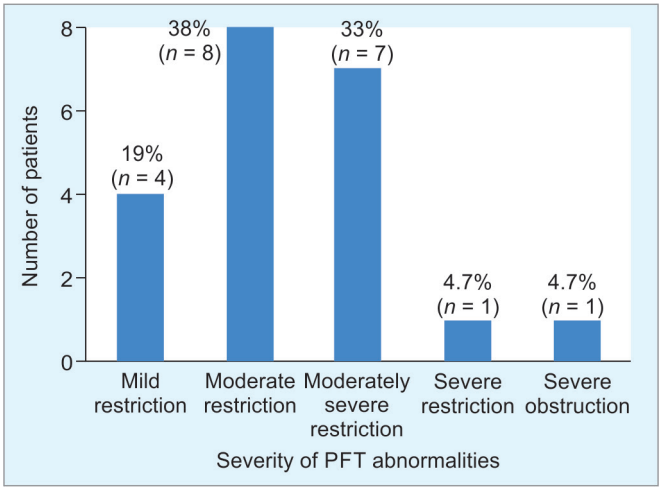


Fig. 1: Bar diagram showing the distribution of severity of PFT in patients with RA

Discussion

Rheumatoid arthritis is a chronic autoimmune inflammatory disease. Pulmonary involvement is one of its common and important extra-articular manifestations. This pulmonary involvement is associated with poor prognosis. Early identification of respiratory dysfunction and appropriate treatment goes a long way in improving the quality of life. The purpose of this observational study was to record the pattern and extent of pulmonary involvement in our part of the globe and, at the same time, make a detailed record of the features that are unique to these areas and features that are shared in common with the other areas of the world.

In the present study, most of the subjects belonged to the fourth and fifth decade of life. Similar observations were noted in studies from India[14,15] and other parts of the world.[16–18] In the present study, women outnumbered men. A similar demographic trend was evident in the studies from India[6] and other parts of the world.[16,18,19] Rheumatoid arthritis most commonly affects women, and there is female predominance. As we had excluded known COPD patients, males were less in proportion in the present study when compared with other studies. In our study, it was observed that in most of the patients, disease duration was less than 2 years, and similar findings were observed in other published studies,[14,20] except for the study[21] from Turkey, where most of the patients had

Table 2: Pulmonary function tests with varied disease severity in patients with RA

PFT	*Remission*	*Low activity*	*Moderate activity*	*Severe activity*
Normal	3	0	15	49
Restrictive	0	1	7	12
Obstructive	0	0	0	1

PFT, pulmonary function testing; RA, rheumatoid arthritis

Table 3: Respiratory abnormalities with varied disease duration in patients with RA

	Abnormal (Symptom/PFT/CXR)	*Normal*	*p-value*
≤2 years	13	40	0.12
>2 years	14	21	

PFT, pulmonary function test; CXR, chest X-ray; RA, rheumatoid arthritis

disease duration of more than 2 years. Among the symptomatic patients in our study, dyspnea was the most common complaint at presentation, followed by cough and wheezing. This is in concordance with the results noted in other published studies.[16,18,22] In the present study, only one person (1.1%) was a former smoker, and the rest all were nonsmokers. Smoking status ranges from 7 to 58% in other published studies.[22,6,23] As the proportion of male patients was relatively lesser in our group, the incidence of smoking in the present study was less than in other published studies. In the present study, 23% were using oral steroids, 11% on methotrexate, and 7% on leflunomide. This contrasts with a study[15] done in Kolkata where most of the patients (76.19%) were taking methotrexate. As most of the patients in our study were denovo detected (77%) with RA at the time of presentation, there was a relatively lower incidence of drug history. In the present study, bilateral basal crepitations (6.8%) and mild hypoxia (1.1%) were noted on examination. Similar findings were observed in other published studies.[22,24] In our study, seropositivity was found in 59% of patients. No statistically significant difference was found between seropositivity and the presence of respiratory abnormalities in our study. Similar observations were found in other studies.[14,17] However, in a study[23] conducted in the United States, it was observed that seropositivity for RF and ACCP was significantly higher in subjects with PFT abnormalities. In the present study, most of the patients with RA had high disease activity (70.5%) followed by moderate activity (25%), remission (3.4%), and low activity (1.1%). However, in other published studies[16,23] from different parts of the world, it was observed that most of the study subjects had low disease activity or were in remission. Most of the patients in these studies were on treatment for RA, which may explain the low disease activity in them.

In the present study that included 88 patients, CXR was normal in most of the patients (95.5%). Unilateral right-sided pleural effusion was evident in 2.3%, followed by bilateral bronchiectasis (1.1%) and bilateral lower-zone reticular thickening (1.1%). In patients with remission and low disease activity, CXR was found to be normal. Majority of patients with moderate (91%) and severe (96.7%) disease activity also had a normal CXR. In another study[24] on the evaluation of pulmonary involvement in RA by radiography and spirometry, it was noticed that hyperinflation (24.8%) was the most common abnormality on CXR, followed by interstitial pattern (14.6%), volume loss (2.4%), and miscellaneous abnormalities (2.8%). Smoking was found in half of the patients included in this study. This study has shown a higher prevalence of CXR abnormalities than other published studies.[18,22] In the present study (n = 88), PFT abnormalities were found in 23.9%, with restrictive pattern (22.7%) being the most common abnormality followed by obstructive pattern (1.1%). The prevalence of PFT abnormalities in the present study was slightly lower than in other published studies.[20,23,24] Smaller sample size in the present study, when compared with other studies,[23,24] lesser incidence of smoking compared with other studies[24] can explain this. In the present study, restrictive pattern was the most common abnormality. A similar trend was observed in other published studies[20,22,24] except for the study[23] conducted in the United States, where the obstructive pattern was the most common type of PFT abnormality. Higher incidence of smokers (58%) in that study might be the reason for the obstructive pattern being the most common pattern. In the present study, small airway disease was found in 33% of patients. The occurrence of small airway disease in RA was also documented in other published studies.[14,16] In the present study, PFT was normal in all the patients with remission. Abnormal patterns of PFT were observed in patients with low-to-moderate activity (34.8%) and high disease activity (26.5%). In our study, higher disease activity (DAS28 ≥5.1) was not found to be significantly associated with the presence of respiratory abnormalities (p = 0.32). However, a statistically significant relationship between disease activity and PFT abnormalities was observed in certain studies[17,18] conducted across different parts of the world.

In our present study, no significant relation was found between the duration of disease and respiratory abnormalities (p = >0.05). Similar observations were noted in other published studies,[14,16] except in a study[15] conducted in Kolkata in which increased disease duration is significantly associated with the presence of spirometry abnormalities. In this study, patients with disease duration of more than 10 years had more spirometry abnormalities.

Conclusion

Our observations conclude that RA patients mostly had restrictive abnormalities on spirometry. Small airway involvement can also occur in RA patients. Chest radiograph abnormalities were detected only in few patients. High index of suspicion regarding the pulmonary involvement in RA is required. A set of questionnaires can be included in routine checkups of RA patients, which can guide them to decide whether a patient should undergo further investigative workup or not to rule out pulmonary involvement.

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