Section: General Medicine

Original Research Article

# ASSESSMENT OF PULMONARY INVOLVEMENT IN RHEUMATOID ARTHRITIS AND ITS RELATIONSHIP WITH DISEASE ACTIVITY

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ABSTRACT

**Background:** Pulmonary involvement is one of the most common extra-articular manifestations of rheumatoid arthritis (RA) and contributes significantly to morbidity and mortality. This study was undertaken to evaluate pulmonary manifestations in patients with RA, regardless of respiratory symptoms and to correlate these manifestations with disease activity.

**Materials and Methods:** A cross-sectional descriptive study was conducted among 50 patients with RA (newly diagnosed or on follow-up) who attended the outpatient department or were admitted to the wards of a tertiary care medical college hospital over a 1-year period. Each patient underwent a detailed history and clinical examination, routine investigations along with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) and pulmonary evaluation with pulmonary function testing (PFT), two-dimensional echocardiography, chest radiography and, where feasible, high-resolution computed tomography (HRCT) of the thorax. Pain was assessed using a visual analogue scale (VAS), functional disability using the Health Assessment Questionnaire (HAQ), and disease activity using the Disease Activity Score 28 (DAS28).

**Results:** The mean age of patients was 46.3 ± 9.75 years, with a female-to-male ratio of 3.2:1. Mean disease duration was 5.18 ± 6.52 years. RF was positive in 39 (78%) patients. Respiratory symptoms were present in 20 (40%) patients, and respiratory signs in 12 (24%) patients. Chest radiographs were abnormal in 13 (26%) patients. HRCT, performed in 30 (60%) patients, was normal in 11 (22%) and showed features of interstitial lung disease (ILD) in 13 (26%). PFT abnormality was seen in 29 (58%) patients — restriction in 22 (44%), obstruction in 6 (12%) and a mixed pattern in 1 (2%). Pulmonary hypertension on echocardiography was found in 7 (14%) patients. Overall, 28 (56%) patients had a pulmonary manifestation, of whom 10 (36%) had no respiratory symptoms. Pulmonary manifestations were significantly correlated with longer RA duration ($p = 0.002$), RF seropositivity ($p < 0.001$), higher HAQ score ($p = 0.049$), and longer duration of methotrexate use ($p = 0.004$), but not with DAS28 score ($p = 0.737$).

**Conclusion:** Pulmonary manifestations were present in more than half of patients with RA, and over a third of these were asymptomatic. Restrictive lung disease was the most common functional abnormality, and HRCT was more sensitive than chest radiography in detecting pulmonary involvement. Given the frequency of subclinical disease, active screening for pulmonary involvement is warranted in all patients with RA, irrespective of respiratory symptoms, particularly those with longer disease duration, seropositivity and greater functional impairment.

**Keywords:** Rheumatoid arthritis; interstitial lung disease; pulmonary function test; disease activity score; extra-articular manifestations; HRCT.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder of unknown cause that affects approximately 0.3–2.1% of the general population, with a female preponderance and peak onset in the third to fifth decades of life.[1,5] While RA principally targets synovial joints, producing a non-suppurative synovitis that can progress to cartilage destruction and joint ankylosis, it frequently involves extra-articular tissues, including the skin, eyes, heart, blood vessels and lungs.[1,2] Extra-articular manifestations occur in nearly 50% of patients with RA and are associated with more severe disease and excess mortality.[3,4,6,7]

Pulmonary involvement is among the most common and clinically significant extra-articular manifestations of RA and represents the second leading cause of death in this population after infection.[8,9] The spectrum of pulmonary disease in RA is broad and includes pleural disease, interstitial lung disease (ILD), rheumatoid nodules, airway disease (bronchiectasis and bronchiolitis), pulmonary hypertension, pulmonary vasculitis, organising pneumonia, and drug-induced lung toxicity from disease-modifying anti-rheumatic drugs (DMARDs).[9] Pleural involvement, though frequent at autopsy (up to 50%), is clinically apparent in only about 10% of cases, underscoring how often pulmonary disease in RA remains subclinical.[13,14] Similarly, the prevalence of ILD in RA ranges from 19% to 44% depending on the diagnostic modality used, with risk factors including male sex, smoking and long-standing disease.[16,17]

Because pulmonary manifestations are often asymptomatic in their early stages, they may go undetected until advanced, irreversible change has occurred. High-resolution computed tomography, pulmonary function testing and echocardiography can identify anatomical and physiological abnormalities that precede overt symptoms, but these investigations are not uniformly available or cost-effective in all settings. Simpler tools such as office spirometry and chest radiography remain widely used first-line screening methods. Given the impact of early detection on prognosis — since RA-associated ILD, unlike idiopathic pulmonary fibrosis, tends to respond more favourably to immunosuppressive therapy — this study was undertaken to characterise pulmonary manifestations in patients with RA, irrespective of respiratory symptoms, and to examine their correlation with disease activity.

**Objectives**

- To study pulmonary manifestations in patients with rheumatoid arthritis.
- To assess the presence of asymptomatic pulmonary involvement.
- To correlate pulmonary involvement with disease activity.

## MATERIALS AND METHODS

This cross-sectional descriptive study was conducted in the Department of General Medicine, Subbaiah Medical College, Shimoga, over a period of one year. Fifty patients with RA — newly diagnosed or on follow-up — who presented to the medicine outpatient department or were admitted to the medical wards were enrolled after obtaining informed consent. All patients were diagnosed as having RA according to the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria.

**Inclusion Criteria**

- Patients diagnosed with RA, either newly or on follow-up.
- Patients are willing to provide informed consent to participate.

**Exclusion Criteria**

- Patients with pre-existing lung disease — chronic obstructive pulmonary disease, pulmonary tuberculosis, bronchiectasis, or bronchial asthma.
- Smokers.
- Patients with thoracic or vertebral (spinal) abnormalities.

**Data collection and evaluation**

All patients underwent a detailed clinical examination with particular attention to the musculoskeletal and respiratory systems, using a structured proforma that recorded demographic details, disease duration, joint involvement, and respiratory symptoms and signs. Pain was assessed using a visual analogue scale (VAS), functional disability using the Health Assessment Questionnaire (HAQ), and disease activity using the Disease Activity Score 28 (DAS28).

The following investigations were performed in all patients: rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pulse oximetry, pulmonary function testing (PFT), chest radiography, and two-dimensional echocardiography. High-resolution computed tomography (HRCT) of the thorax was performed where clinically indicated and feasible.

**Statistical Analysis**

Data were analysed using SPSS version 18 software. Student's t-test was used to compare means of numerical data between groups, the chi-square test was used to assess associations between categorical variables, and regression analysis was used to assess correlations between continuous variables. A p-value $< 0.05$ was considered statistically significant.

## RESULTS

Fifty patients with RA, either newly diagnosed or on follow-up, were enrolled over the one-year study period.

**Demographic and disease characteristics**

The age of study participants ranged from 22 to 64 years, with a mean age of 46.3 ± 9.75 years. Of the 50 patients, 38 (76%) were female, and 12 (24%) were male, giving a female-to-male ratio of 3.2:1. Mean age was 45.22 ± 10.26 years in females and 48.83 ± 9.58 years in males; although males were older on average, this difference was not statistically significant (p = 0.286).

Mean duration of RA was 5.18 ± 6.52 years (range 1–26 years), and was longer in females (5.53 ± 7.20 years) than males (4.08 ± 3.60 years), though this difference was not statistically significant (p = 0.507). All patients had early morning stiffness, with a mean duration of 133.6 ± 72.33 minutes. The mean number of joints involved was 31.64 ± 7.66 (range 10–42), comprising 24.28 ± 6.06 small joints and 7.32 ± 2.08 large joints. Joint deformities were present in 15 (30%) patients, most commonly swan-neck deformity (13 patients) and Boutonnière deformity (9 patients). None of the patients had clinically detectable rheumatoid nodules.

RF was positive in 39 (78%) patients — 29 (58%) females and 10 (20%) males; a numerically higher proportion of males were seropositive (83.3% vs. 76.3% in females), but this was not statistically significant (p = 0.15). ACPA was positive in 47 (94%) patients. Mean ESR was 48.12 ± 29.08 mm/hr, with an elevated ESR seen in 40 (80%) patients.

**Respiratory symptoms and signs**

Twenty (40%) patients reported respiratory symptoms: cough in 18 (36%) patients (of whom 4 also had expectoration), breathlessness in 12 (24%) patients, and chest pain in 4 (8%) patients; none had haemoptysis. Of those with cough, 12 had chronic cough, 3 subacute and 3 acute. Respiratory signs were detected on examination in 12 (24%) of the 50 patients.

**Radiological and functional findings**

Chest radiography was abnormal in 13 (26%) patients, with reticular opacities being the commonest abnormality (5 patients, 10%), followed by honeycombing (3 patients, 6%), bilateral lower zone infiltrates (2 patients, 4%), and single cases each of fibrosis, obliteration of the costophrenic angle, and prominent bronchovascular markings. Mean duration of RA was significantly longer in patients with an abnormal chest radiograph than in those with a normal radiograph (p < 0.001).

HRCT of the thorax was performed in 30 (60%) patients — the remaining 20 could not undergo the scan owing to eligibility and cost constraints under the institutional health scheme. Among those scanned, 11 (22% of the cohort) had a normal HRCT, while 13 (26%) showed features suggestive of ILD, 2 (4%) had pleural thickening, 2 (4%) had minimal pleural effusion, 1 (2%) had obliterative bronchiolitis, and 1 (2%) had panacinar/paraseptal emphysema. HRCT identified abnormalities in a higher proportion of patients than chest radiography, consistent with its greater sensitivity for early or subclinical parenchymal disease.

PFT abnormality was found in 29 (58%) patients: a restrictive pattern in 22 (44%), an obstructive pattern in 6 (12%), and a mixed pattern in 1 (2%). Restrictive disease was thus the predominant functional abnormality. Two-dimensional echocardiography, performed in all patients to screen for pulmonary hypertension, showed pulmonary hypertension in 7 (14%) patients, while 43 (86%) had no evidence of pulmonary hypertension.

**Overall prevalence and pattern of pulmonary manifestations**

Taking together abnormalities on PFT, HRCT, chest radiography, and echocardiography, 28 (56%) of the 50 patients studied had at least one pulmonary manifestation identified by the end of the study. The pattern comprised restrictive PFT abnormality alone in 18%, ILD in 26%, ILD with pulmonary hypertension in 14%, paraseptal emphysema in 2%, minimal pleural effusion in 4%, pleural thickening in 4%, and obliterative bronchiolitis in 2%. Notably, 10 of the 28 patients (36%) with a pulmonary manifestation had no respiratory symptoms whatsoever, highlighting a substantial burden of subclinical disease.

**Table 1: Prevalence and pattern of pulmonary manifestations in the study population (n = 50)**

| **No pulmonary manifestation** | **22** | **44.0%** |
|---|---|---|
| Restrictive PFT abnormality (isolated) | 9 | 18.0% |
| Interstitial lung disease (ILD) | 13 | 26.0% |
| ILD with pulmonary hypertension | 7 | 14.0% |
| Minimal pleural effusion | 2 | 4.0% |
| Pleural thickening | 2 | 4.0% |
| Paraseptal emphysema | 1 | 2.0% |
| Obliterative bronchiolitis | 1 | 2.0% |

**Correlates of pulmonary manifestations**

Patients with pulmonary manifestations were significantly older (49.68 ± 8.97 years) than those without (42.00 ± 9.17 years; p = 0.005). Mean RA duration was significantly longer in patients with pulmonary manifestations (7.64 ± 7.84 years) than in those without (2.05 ± 1.36 years; p = 0.002). RF positivity was significantly more frequent among patients with pulmonary manifestations (27/28, 96%) than among those without (12/22, 56%; p < 0.001). Mean HAQ score was significantly higher in patients with pulmonary manifestations than in those without (p = 0.049), and mean duration of methotrexate use was significantly longer in patients with pulmonary manifestations (7.0 years) than in those without (2.8 years; p = 0.004).

In contrast, EULAR/DAS28 disease activity scores, VAS pain scores, CRP and ESR were all numerically higher in patients with pulmonary manifestations, but none of these differences reached statistical significance (DAS28: p = 0.737; VAS: p = 0.273; CRP: p = 0.149; ESR: p = 0.121).

The presence of respiratory symptoms showed a significant overall association with pulmonary manifestations (p = 0.042), but — as noted above — more than a third of patients with pulmonary involvement were symptom-free.

**Table 2: Comparison of clinical and laboratory parameters between patients with and without pulmonary manifestations**

| **Age (years), mean ± SD** | **42.00 ± 9.17** | **49.68 ± 8.97** | **0.005** |
|---|---|---|---|
| Duration of RA (years), mean ± SD | 2.05 ± 1.36 | 7.64 ± 7.84 | 0.002 |
| RF positivity, n (%) | 12 (56%) | 27 (96%) | <0.001 |
| HAQ score, mean ± SD | 0.91 | 0.97 | 0.049 |
| DAS28 score, mean ± SD | 5.6 ± 1.9 | 5.8 ± 2.2 | 0.737 |
| Duration of methotrexate use (years) | 2.8 | 7.0 | 0.004 |

## DISCUSSION

In this cross-sectional study of 50 patients with RA, pulmonary manifestations were identified in more than half (56%) of the cohort, consistent with the well-recognised burden of thoracic involvement in RA reported in the literature.[8,9] The demographic profile of the study population — mean age 46.3 years and a female-to-male ratio of 3.2:1 — closely mirrored earlier Indian series, including those by Kulkarni AA (mean age 46.5 years) and Raniga S et al. (female-to-male ratio 3:1), and fell within the range of 2:1 to 4:1 reported in most studies of RA epidemiology.[cf. discussion in thesis]

A key finding of this study was that 36% of patients with a pulmonary manifestation were entirely asymptomatic — a proportion consistent with the report by Mary Iyaly, in which just over half of patients with respiratory involvement lacked respiratory symptoms. This is plausibly explained by the restricted physical activity that many RA patients experience because of joint disease, which may mask or delay the perception of dyspnoea. This finding reinforces the case for proactive pulmonary screening in RA rather than a purely symptom-triggered approach.

Restrictive lung disease was the predominant functional abnormality on PFT (44% of the cohort), consistent with the pattern typically described in RA-associated interstitial lung disease, and HRCT proved considerably more sensitive than chest radiography for detecting pulmonary involvement — identifying abnormalities, including early ILD, in patients whose chest radiographs were normal. This mirrors the well-established observation that radiographic changes in RA-ILD often lag behind HRCT findings by months to years.

Pulmonary manifestations correlated strongly with longer RA duration and RF seropositivity, both readily identifiable clinical markers that may help target screening to higher-risk patients. The association between seropositivity and pulmonary involvement is biologically plausible, as anti-citrullinated protein antibodies and rheumatoid factor have been implicated in the pathogenesis of RA-associated ILD, and is consistent with earlier work by Derksen van Zeben et al., who found that RF-positive patients had more extra-articular manifestations and greater disease severity generally. The significant association with longer duration of methotrexate use likely reflects, at least in part, the confounding effect of longer disease duration itself, since patients with more prolonged RA were more likely to have been treated with methotrexate for longer; a causal contribution of methotrexate-induced pneumonitis cannot be excluded and would require a study design capable of distinguishing drug toxicity from disease progression.

Somewhat unexpectedly, the DAS28 disease activity score did not correlate significantly with the presence of pulmonary manifestations, although the mean DAS28 was numerically higher in the group with pulmonary involvement. This finding is consistent with reports by Metafratzi ZM et al. and Mary Iyaly, though it contrasts with the study by Habib HM et al., which — in a considerably larger cohort — found a significant positive correlation between pulmonary manifestations and DAS28. The absence of a significant correlation in the present study is most plausibly attributable to the modest sample size and to the fact that many patients were relatively early in their treatment course at the study institution, with disease activity still being actively optimised at the time of assessment.

**Limitations**

- The relatively small sample size (n = 50) limited the statistical power to detect correlations, particularly with disease activity.
- Some patients with a short duration of respiratory symptoms were included, which may have influenced the apparent prevalence of symptoms.
- Many patients were on relatively short follow-up at the study institution, with treatment still being optimised, which may have affected the measured disease activity.
- HRCT was not performed in all patients (only 60% of the cohort), which may have led to underestimation of the true prevalence of interstitial lung disease.

- Because this was a cross-sectional study, causal relationships among RA, its treatment, and pulmonary manifestations could not be established.

## CONCLUSION

Pulmonary manifestations were present in more than half (56%) of patients with rheumatoid arthritis in this cohort, and more than a third of these patients had no respiratory symptoms — underscoring the substantial burden of clinically silent lung disease in RA. Restrictive lung disease was the most common functional abnormality, and HRCT detected pulmonary involvement more consistently than chest radiography. Pulmonary manifestations increased significantly with longer disease duration, higher functional disability (HAQ score), rheumatoid factor seropositivity, and longer methotrexate therapy duration, but did not correlate significantly with DAS28-defined disease activity in this sample. These findings support routine, proactive screening for pulmonary involvement — including PFT and, where feasible, HRCT — in all patients with RA, irrespective of respiratory symptoms, with particular attention to those with long-standing, seropositive disease and greater functional impairment, given the potential for earlier diagnosis to favourably influence treatment and outcomes.

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