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Pulmonary Manifestations in Rheumatoid Arthritis: A Prospective Study of Prevalence, Risk Factors, and Treatment Outcomes

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Abstract

Aims: Current screening paradigms for RA-associated lung disease lack validated serologic thresholds, while treatment remains guideline-agnostic with limited comparative effectiveness data. This prospective study aimed to: (1) establish clinically actionable risk thresholds (anti-CCP, DAS-28), (2) characterize HRCT patterns, and (3) compare mycophenolate vs conventional immunosuppressants. This study aimed to characterize pulmonary involvement in RA, identify ILD risk factors, and assess 6-month treatment outcomes to address these unmet needs. ***Methods:*** This prospective observational study (2019-2021) enrolled 65 RA patients (ACR/EULAR criteria) with pulmonary symptoms at a tertiary center. Comprehensive evaluation included HRCT (UIP/NSIP patterns), PFTs, 6-minute walk test (6MWT), DAS-28 scoring, and serology (RF/anti-CCP). Statistical analysis used Mann-Whitney and Pearson χ^2 tests. ***Results:*** - ILD prevalence: 40% (UIP:76.9%, NSIP:23%); bronchiectasis:21.5%; pleural effusion: 21.5%.

- Significant predictors:
  - Age >50 years (OR 3.2, p<0.01);
  - RA duration >8 years (OR 4.1, p<0.001)
  - Anti-CCP >150 U/ml (OR 5.6, p<0.001)
  - DAS-28 >5.1 (OR 3.8, p=0.002)
- Mortality: 19.2% in ILD vs 2.5% non-ILD (p=0.037)
- 6MWT: 26.2% desaturation at baseline
- Treatment: Mycophenolate mofetil superior to cyclophosphamide/corticosteroids (p=0.004)

Conclusions: This study confirms the high burden of pulmonary disease in RA (particularly UIP-pattern ILD) and provides actionable thresholds for risk stratification (anti-CCP >150 U/ml, DAS-28 >5.1). Mycophenolate mofetil emerges as a preferred therapeutic option, supporting the need for revised management guidelines.

Keywords: ***Rheumatoid arthritis, Interstitial lung disease, Usual interstitial pneumonia, Mycophenolate mofetil, Disease Activity Score.***

Introduction

Pulmonary complications are being recognized as a major source of morbidity and mortality in rheumatoid arthritis (RA), second only to cardiovascular disease [1]. Among these, interstitial lung disease (ILD) is the most severe extra-articular manifestation, which contributes significantly to functional decline, hospitalization, and death. Yet, despite its clinical impact, RA-ILD remains underdiagnosed, poorly risk-stratified, and lacking in disease-specific therapeutic evidence.

A growing body of research highlights the prevalence of both clinical and subclinical ILD across the RA disease spectrum. Gabbay *et al.* found that 33% of early RA patients had HRCT evidence of ILD, despite only 14% reporting respiratory symptoms [2]. Kim *et al.* showed that RA-ILD patients with a definite usual interstitial pneumonia (UIP) pattern had a median survival of just 3.2 years, compared to 6.6 years in those without UIP [3]. The frequent subclinical onset and delayed recognition with poor prognosis underscore the need for proactive screening strategies.

Moreover, ILD may not merely be a complication but an initiating site of RA pathogenesis. McDermott *et al.* suggest that pulmonary inflammation and anti-citrullinated protein antibody (ACPA) production in the lungs may precede joint disease [4].

Accurate diagnosis and prognostication of RA-ILD are further complicated by radiological and histopathological heterogeneity. However, HRCT interpretation remains variable; a

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Fleischner Society study involving 1,149 scans reported a 22-38% disagreement rate among radiologists in classifying UIP vs. NSIP patterns [5].

Serologic markers, particularly anti-CCP antibodies, have emerged as promising tools for risk prediction. A meta-analysis of 29 studies (n = 10,158) confirmed a strong association between anti-CCP positivity and RA-ILD (OR 2.10, 95% CI: 1.64-2.69), though thresholds predictive of ILD remain undefined [6].

On the therapeutic front, evidence remains sparse and largely extrapolated from non-RA populations. For example, the RECITAL trial (NEJM 2023) showed comparable outcomes between rituximab and cyclophosphamide in CTD-ILD but excluded RA-specific analysis [7]. There is minimal prospective data comparing immunosuppressive options in RA-ILD, especially for agents like mycophenolate mofetil (MMF), which are increasingly used in practice.

Thus, despite the growing recognition of interstitial lung disease (ILD) as a major contributor to morbidity and mortality in rheumatoid arthritis (RA), several critical challenges remain. Current diagnostic practices struggle with variability in radiologic interpretation, while serological risk stratification particularly regarding anti-CCP antibody thresholds lacks clarity. Moreover, treatment strategies are extrapolated from broader connective tissue disease cohorts, with little prospective evidence directly comparing immunosuppressive options such as mycophenolate mofetil (MMF) and cyclophosphamide specifically in RA-ILD.

This study was therefore designed to address these pressing evidence gaps through a focused prospective investigation.

Materials and Methods

This prospective observational study was conducted at a tertiary care hospital, enrolling patients from the General Medicine and Rheumatology outpatient departments and inpatient wards between October 2019 and March 2021. The sample size was calculated based on an assumed 45% prevalence of pulmonary manifestations in rheumatoid arthritis, with 10% absolute precision and a 95% confidence interval, yielding a required sample size of 96. However, due to feasibility constraints, 65 consecutive eligible patients were ultimately enrolled.

Inclusion criteria were: age above 18 years, a diagnosis of rheumatoid arthritis according to the 2010 ACR/EULAR criteria, and at least one feature suggestive of pulmonary involvement. These included pulmonary symptoms such as dyspnea, cough, chest pain, wheeze, or hemoptysis; signs like rales, clubbing, or cyanosis; a positive 6-minute walk test defined by desaturation (SpO_2 drop ≥4%); or abnormal findings on imaging or ECG suggestive of pulmonary disease. Exclusion criteria included the presence of other pulmonary conditions such as asthma or COPD, seronegative rheumatoid arthritis, active respiratory infections, pregnancy, and overlap or mixed connective tissue disorders.

The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment. Patient confidentiality was strictly maintained throughout the study. As this was a non-interventional study, no additional investigations or procedures were performed beyond routine clinical care advised by the treating physicians.

Data analysis was performed using SPSS version 21.0 (IBM). Descriptive statistics, including means, standard deviations, and proportions, were used to summarize baseline characteristics. Chi-square tests and Mann-Whitney U tests were applied for comparison of categorical and non-parametric variables, respectively. Correlations between continuous variables were analyzed using Pearson or Spearman correlation coefficients, as appropriate. Logistic regression analysis was used to identify independent risk factors for pulmonary involvement. Associations between high-resolution computed tomography (HRCT) findings and pulmonary function test (PFT) results were assessed using analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant.

Results

Demographic Characteristics

Sixty-five patients with rheumatoid arthritis and pulmonary manifestations were included in the study. The mean age was 49.32 ± 10.92 years, with patients ranging from 30 to 70 years. The majority of patients (29.2%) were in the 41-50 age group, followed by 27.7% in the 30-40 age group, and 21.5% each in the 51-60 and over 60 age groups. Females constituted 60% of the cohort and males 40%, with a male-to-female ratio of 1:1.5. The mean duration of rheumatoid arthritis symptoms at the time of pulmonary disease diagnosis was 8.54 ± 4.56 years.

Clinical Features

All patients presented with at least one respiratory symptom, the most common being cough (75.38%), followed by dyspnea (56.92%). On physical examination, crepitations were detected in 40% of patients at the first visit, including all those diagnosed with interstitial lung disease (RA-ILD). Clubbing was observed in 7.7% of patients at the first visit, 8.62% at the second visit, and 7.41% at the third.

6-Minute Walk Test (6MWT)

At baseline, 26.2% of patients experienced desaturation, defined as a drop in oxygen saturation of ≥4%, while 3.1% were unable to perform the test due to resting hypoxia or tachypnea. At the 3-month follow-up, desaturation was noted in 19% of patients, and 15.5% could not perform the test. At 6 months, 22.2% demonstrated desaturation, and 1.9% remained unable to complete the test.

Arterial Blood Gas (ABG) Analysis

Hypoxemia, defined as PaO_2 <60 mmHg, was present in 10.8% of patients at baseline, 12% at the 3-month follow-up, and 5.5% at 6 months. Respiratory alkalosis was observed in 5.1% at baseline and in 1.8% at 6 months.

Laboratory Findings

The mean erythrocyte sedimentation rate (ESR) at presentation was 48.68 ± 20.96 mm/hr, and the mean C-reactive protein (CRP) level was 14.47 ± 24.5 mg/L. Rheumatoid factor was positive in all patients (100%), while anti-cyclic citrullinated peptide (anti-CCP) antibodies were positive in 76.9% of the cohort.

HRCT Findings

High-resolution computed tomography (HRCT) scans were abnormal in 89.2% of patients (n=58), while 10.7% (n=7) had normal HRCT findings. Interstitial lung disease was detected in 26 patients (44.8%), with usual interstitial pneumonia (UIP) as the predominant pattern (76.9%), followed by nonspecific interstitial pneumonia (NSIP) in 23.0%. Advanced pulmonary disease in the form of secondary pulmonary hypertension was seen in 26.9% of UIP cases and in 12.8% of patients with non-ILD lung disease. Bronchiectasis and pleural effusion were each observed in 21.5% of patients, while solitary pulmonary nodules and bronchopleural fistula were noted in 4.6% and 1.5%, respectively.

Pulmonary Function Test (PFT) Findings

Of the 34 patients with available PFT data, seven patients with normal HRCT scans demonstrated an obstructive pattern. A predominantly restrictive pattern was seen in those with RA-ILD, though some exhibited a mixed pattern. PFT results were unavailable in 31 patients, which was a limitation.

Risk Factor Analysis

The median age of patients with ILD was 58 years, whereas the median age in those with non-ILD lung disease was 45 years. This difference was statistically significant (Mann-Whitney U test, $p<0.05$). The male-to-female ratio in the ILD group was 16:10, compared to 10:29 in the non-ILD group, and this difference was also significant (Chi-square test, $p=0.004$). The median duration of rheumatoid arthritis in patients with ILD was 11 years, compared to 6 years in those with other pulmonary manifestations ($p<0.001$). The mean Disease Activity Score (DAS28) at presentation was significantly higher in the ILD group (5.6) than in the non-ILD group (4.3), with a p-value of 0.001. Rheumatoid factor and anti-CCP titres were significantly elevated in the RA-ILD group, with RF titres exceeding 1:64 and a median anti-CCP level of 163 U/ml ($p<0.001$ for both).

Mortality Outcomes

During the 6-month follow-up, five patients with RA-ILD (19.2%) died due to respiratory failure, compared to one death (2.5%) in the non-ILD group. This difference was statistically significant ($p=0.037$).

Treatment Outcomes

Among the RA-ILD patients, 10 received mycophenolate mofetil, five received cyclophosphamide, four received corticosteroids, three received baricitinib, and four continued methotrexate without additional ILD-specific therapy. Prognosis was significantly better in patients who received mycophenolate mofetil ($p=0.004$).

Discussion

In this study of 65 RA patients with pulmonary involvement, the mean age was 49.3 ± 10.9 years, slightly younger than that reported by Bilgici *et al.* (mean age 53.6 years), possibly reflecting population differences or earlier detection [8].

Although females predominated overall (60%), ILD was more common in males (M:F = 1.6:1), consistent with prior findings by Gabbay E *et al.* [9].

The mean RA duration before pulmonary involvement was 8.5 years, comparable to Bilgici *et al.*'s report of 8.4 years, underscoring the typically delayed onset of extra-articular disease [8].

Cough (75.4%) and dyspnea (56.9%) were the most frequent symptoms, in line with a Saudi study by Boudal *et al.*, which reported cough (55.6%) and dyspnea (30.2%) in RA-ILD patients. Clinical signs such as crepitations (40%) and clubbing (8%) were also common, though at a lower frequency than in some other cohorts. These findings emphasize the utility of respiratory symptom screening, even when subtle, to facilitate early diagnosis.

HRCT findings showed a UIP pattern in 44.8% and NSIP in 23% of RA-ILD patients, aligning with existing literature where UIP predominates in 40-65% of cases. UIP is associated with worse prognosis due to fibrotic progression and traction bronchiectasis, while NSIP tends to follow a more benign course [10]. Differentiation on imaging may be challenging in early stages and could require histopathologic confirmation.

Pulmonary function tests complemented imaging by identifying physiologic impairment. As expected, restrictive patterns were predominant among RA-ILD cases. Notably, seven patients with normal HRCT scans demonstrated obstructive PFT patterns, indicating early or small airway disease not radiologically evident. Mori *et al.* reported similar findings, with 30.3% of RA patients showing small airway dysfunction without HRCT abnormalities [11]. These results advocate for combined radiological and functional assessment to improve diagnostic yield.

Mortality in our cohort was significantly higher in the RA-ILD group (19.2%) compared to non-ILD patients (2.5%) ($p = 0.037$). All deceased ILD patients had a UIP pattern. Lee *et al.* similarly reported higher all-cause mortality and pulmonary hypertension among UIP-pattern RA-ILD patients, reinforcing the pattern's prognostic significance [12]. Although NSIP generally confers better outcomes, the short follow-up in our study limits direct comparison of long-term survival between subtypes.

Several clinical and serological features were significantly associated with ILD in RA. The median age in the ILD group was 58 years versus 45 years in non-ILD ($p < 0.05$). Male sex ($p = 0.004$), longer RA duration (11 vs. 6 years, $p < 0.001$), and higher disease activity (DAS28: 5.6 vs. 4.3, $p = 0.001$) were all strongly associated with ILD. All patients were RF positive, and 76.9% were anti-CCP positive, with significantly higher RF titres (>1:64) and anti-CCP levels (median: 163 U/ml) in the ILD group ($p < 0.001$). These findings corroborate with a review by Kamiya H *et al.*, who highlighted high-titre ACPA as an independent predictor of ILD [6]. Together, these variables define a reproducible high-risk phenotype for RA-ILD, justifying early screening in older, seropositive males with high disease activity or long-standing RA.

Among therapeutic options, mycophenolate mofetil (MMF) was associated with better short-term outcomes in our cohort ($p = 0.004$). Among therapeutic options, mycophenolate mofetil (MMF) was associated with better short-term outcomes in our cohort ($p = 0.004$). However, a 2024 systematic review by Lombardi *et al.* concluded that evidence from randomized trials on MMF or azathioprine in ILD remains of very low certainty. While MMF may support preservation of lung function, confidence in its benefit is limited. Cassone *et al.*, in a separate review, presented contrasting findings, further underscoring the absence of consensus regarding MMF efficacy in RA-ILD [13]. Our study aims to contribute to this ongoing debate.

Cyclophosphamide, used in five patients, was less effective and carries known risks including cytopenias and infections, raising concerns about its long-term tolerability. There are no controlled clinical trials for Cyclophosphamide in RA-ILD, but it is used in clinical practice despite its limited efficacy data, especially in the case of rapidly progressive ILD. As noted by Innabi *et al.*, the available evidence is limited to small retrospective case series without comparative groups, and outcomes have been inconsistent [14]. There is currently no robust evidence to support cyclophosphamide's benefit in AE-ILD, and well-designed randomized controlled trials are needed to better define its role.

Corticosteroids may provide transient benefit in inflammatory subtypes (e.g., NSIP), but offer limited efficacy in fibrotic disease and increase the risk of opportunistic infections.

Methotrexate, historically implicated in pulmonary toxicity, did not worsen outcomes in our patients. This supports findings by Juge *et al.*, who found no increased RA-ILD risk with MTX, and even reported delayed ILD onset in MTX-treated patients.

Baricitinib was used in three patients, with stable lung function observed. While promising, evidence for JAK inhibitors in RA-ILD is still emerging. In our cohort, baricitinib was administered

to three patients with RA-ILD, all of whom demonstrated stable lung function during follow-up. While this finding is promising, the broader role of Janus kinase inhibitors (JAKis) in RA-ILD is still under active investigation. As Harrington *et al.* noted, concerns about cardiovascular and thromboembolic risks mean that JAK is are best reserved for younger patients without significant comorbidities and in those with refractory disease unresponsive to multiple biologic DMARDs [15]. Until long-term surveillance studies, such as the FDA-mandated post-marketing safety study for baricitinib (NCT03915964), are completed, the cautious, case-by-case use of JAKis in RA-ILD is advisable.

Overall, MMF appears to offer the most favorable balance between efficacy and safety, though larger RCTs are needed to validate treatment algorithms.

This study has several limitations. Due to the COVID-19 pandemic, only 65 patients were enrolled versus the targeted 96. The follow-up period of six months was insufficient to assess long-term outcomes or mortality predictors. As an observational study, therapeutic efficacy comparisons lack the rigor of randomized controlled trials. Moreover, HRCT was the sole modality used for ILD classification; no histopathologic confirmation was obtained.

Conclusion

To conclude, the study offers valuable insights into pulmonary manifestations in RA. Interstitial lung disease, especially the UIP pattern, was the most frequent and severe subtype identified. RA-ILD was significantly associated with older age, male sex, longer disease duration, higher disease activity scores, and elevated RF and anti-CCP titres. The presence of obstructive PFT patterns in patients with normal HRCT scans highlights the need for combined.

Declarations

Human subjects

Consent for treatment and open access publication was obtained or waived by all participants in this study. Seth GSMC Medical College and King Edward Memorial Hospital issued approval IEC/DISS/118/19. The IEC-II hereby approves the proposal entitled Protocol version no. 1.2

Animal subjects

All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest

None

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Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years 9 of 10 with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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