

# Interstitial Lung Disease and its Associations in Rheumatoid Arthritis: Data from a District General Hospital in Sri Lanka

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## ABSTRACT

**CONTEXT:** Interstitial lung disease (ILD) is a frequent pulmonary manifestation of rheumatoid arthritis (RA). No Sri Lankan studies have determined the prevalence of lung disease in RA and its associations.

**AIMS:** To find the prevalence of ILD in RA and its association with rheumatoid factor (RF), erosions, Disease activity score in 28 joints (DAS 28), disease duration, Body mass index (BMI), erythrocyte sedimentation rate (ESR), smoking, and also to determine the prevalence of lung disease with demographic factors like age, sex, and income.

**SETTINGS AND DESIGN:** Questionnaire based retrospective study at a District General Hospital in Sri Lanka.

**MATERIALS AND METHODS:** Diagnosed RA patients included through convenient sampling as it was a simple method that could facilitate data collection in a short duration. Since all patients with a diagnosis of RA were eligible, all consecutive patients with a diagnosis of RA at the rheumatology clinics were included in the study. To reduce the bias a large sample of patients were used as well as patients attending different rheumatology clinics were included and also patients who were referred to the hospital from peripheries were included in the study. The calculated sample size was 384 and according to patient numbers attending clinics, a period of 6 months was decided to select the study sample.

**STATISTICAL ANALYSIS USED:** Chi-Square calculation and logistic regression analysis using Minitab 17 software.

**RESULTS:** From 384 patients, the prevalence of ILD was 14.58%, been 5.4% in early RA (<2 years disease duration). Mean age of ILD group was 52.94 years (95% CI 64.66-41.22). Mean RA duration was 7.69 years (95% CI, 2.38-12.99). Male to female sex ratio of RA was 1:7, and that of ILD was 2:9. DAS 28 was 4.58 (95% CI, 3.48-5.68). Statistically significant associations were noted with ILD and DAS 28 ( $P = .0006$ ), ESR ( $P = .005$ ), RF ( $P = .03$ ), erosions ( $P < .00001$ ), and smoking ( $P < .05$ ). Mean BMI was 22.67 kg and 75.78% had low income (<50000 rupees/month = 327 US \$).

**CONCLUSIONS:** ILD significantly associates RA severity indices like DAS 28, ESR, erosions, RF, and also with smoking. No significant association was found with BMI or gender difference. Therefore, disease severity indices could be used to predict progression to ILD in RA.

**KEYWORDS:** Rheumatoid arthritis, interstitial lung disease, high-resolution computed tomography, erosions, Rheumatoid factor

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## Introduction

Interstitial lung disease (ILD) is the commonest lung manifestation of rheumatoid arthritis (RA).<sup>1</sup> The documented prevalence of ILD in RA varies according to the criteria used to define the disease, methods of detection and reporting, with low rates from chest X-ray (CXR) abnormalities to 41% based on abnormal physiology and up to 71% from the presence of alveolitis.<sup>2,3</sup> Clinical detection has been reported to be <5% using plain chest X-ray alone.<sup>4</sup> However, ILD might be the only presenting manifestation of systemic disease in up to 15% of patients.<sup>5</sup>

ILD in RA is often asymptomatic initially. Documented risk factors for developing ILD in RA include male gender,<sup>6</sup> smoking,<sup>7</sup> RF and anti-cyclic citrullinated peptide (CCP) positivity,<sup>8-10</sup> and long standing disease duration of RA.<sup>11</sup>

Although some extra-articular manifestations of RA have decreased with advances in therapy, the incidence of ILD has remained fairly stable,<sup>12,13</sup> if not increased.<sup>14</sup>

The risk of death for RA patients with ILD was 3 times higher than in RA patients without ILD with a median survival after ILD diagnosis of only 2.6 years. ILD contributed ~13% to the excess mortality of RA patients when compared with the general population.<sup>15</sup>

Current study was carried out to find out the prevalence of ILD in RA in Sri Lanka, as it's a known risk factor to increase motility in RA, and also to find the association of ILD in RA with disease duration, disease activity score in 28 joints (DAS 28), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), smoking, and presence of erosions in hand X-rays.



Questionnaire also assessed prevalence of ILD with age, sex, and income of patients.

## Subjects and Methods

Data were collected from a District General Hospital in Sri Lanka. Consenting, diagnosed RA patients (according to 1987 ARA criteria or 2010 ACR/EULAR Classification Criteria for RA) were selected over 6 months. Non consenting patients (22) and ones with previous or current history of Tuberculosis (TB) were excluded (6 patients), as tuberculosis mimics the clinical and radiological features of many ILDs, leading to diagnostic errors and delays.<sup>16</sup>

Formula used to determine the sample size was<sup>17</sup>:

$$s = X^2 NP(1-P) \div d^2 ((N-1)1 + X^2 P^2(1-P))$$

$s$  = required sample size.

$X^2$  = the table value of chi-square for 1 degree of freedom at the desired confidence level

(3.841).

$N$  = the population size.

$P$  = the population proportion (assumed to be .50 since this would provide the maximum sample size).

$d$  = the degree of accuracy expressed as a proportion (.05).

Accordingly, as there were no Sri Lankan studies done to find the prevalence of ILD in RA the prevalence was considered as 50% to provide maximum sample size.

A sample of 384 was selected by convenient sampling with selection of consecutive clinic patients with RA and a duration of 6 months considered to obtain the necessary number of cases according to daily clinic visits. By selecting a large sample and also by including patients referred to hospital from peripheries we tried to minimize the bias seen in convenient sampling. Information was obtained from patients themselves, their hospital and clinic files, the hospital laboratory system, and from questionnaires which was completed by a trained doctor.

Demographic variables such as age, race, smoking history, and monthly income status were recorded together with presence of other illness, such as diabetes mellitus (DM), hypertension, Asthma (BA), chronic obstructive pulmonary disease (COPD), and time since diagnosis were recorded.

Patients with examination findings (velcro crackles, finger clubbing, 6-minute walk tests to detect the presence of oxygen desaturation on ambulation) or CXR features of lung involvement were referred to a chest physician who arranged HRCT of the chest. All CXR and HRCT scans were reported by a consultant radiologist. CXR features of pleural effusion together with positive HRCT findings, such as lower zone predominant reticular or reticulo-nodular pattern and features of effusion, ground glass densities, honeycombing, traction bronchiectasis, or interlobular septal thickening and rheumatoid nodules were considered positive findings. Pleural effusions occur in patients with various forms of interstitial lung disease.<sup>18</sup> Hence, patients with pleural effusions detected by CXR

detected by CXR were also referred to a chest physician for further assessment. Early RA was considered as 24 months or less, with greater emphasis on the first 12 months.<sup>19</sup>

Chi-Square calculation was used in calculating association of ILD and smoking, erosions and sex difference, while logistic regression analysis was used in calculating associations between prevalence of lung disease, DAS 28, ESR, and BMI. Only rheumatoid factor availability was documented as it was carried out by the hospital lab and anti CCP antibodies were not available in the government hospital setting due to the high cost. Analysis was done using Minitab 17 statistical software.

## Results

From a total of 384 patients 56 had CXR and/or HRCT features of ILD (CXR-12, HRCT-56). The number of patients with ILD before 2 years of disease duration (early RA) was 21. Hence, the prevalence of lung disease in early RA was 5.4% while the prevalence in the total sample was 14.58%.

Mean age of the sample of ILD was 52.94 years (95% CI, 64.66-41.22).

Its mean RA duration was 7.69 years (95% CI, 2.38-12.99).

Association between duration of RA and lung disease was significant with  $P < .05$

Cohort had 46 males and 338 females with a female to male ratio of 7:1. However, the sex ratio of the ILD sample was 9:2.

Significant associations ( $P < 0.05$ ) were seen between prev-

| VARIABLE                     | PATIENTS WITH ILD (N=56) | P VALUE ( $P < .05$ SIGNIFICANT) |
|------------------------------|--------------------------|----------------------------------|
| Rheumatoid factor positivity | 44 (78.571%)             | .030264                          |
| Female sex                   | 47 (83.928%)             | .307528                          |
| Male sex                     | 9 (16.071%)              | .307528                          |
| Presence of erosions         | 52 (92.857%)             | <.00001                          |
| Smoking                      | 16 (28.571%)             | <.00001                          |

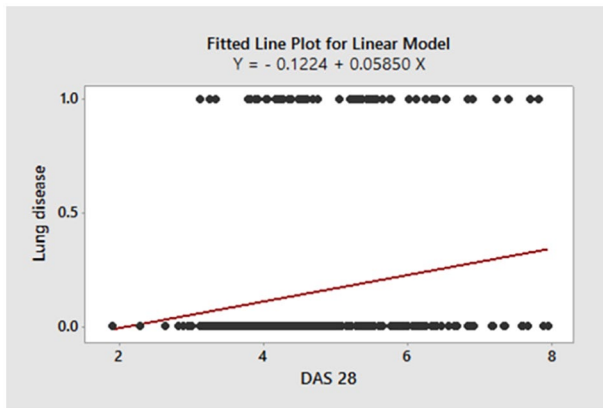
alence of ILD and RF, presence of erosions, and with smoking.

A weak positive correlation ( $r = .18$ ) was seen between DAS 28 and lung disease (Figure 1).

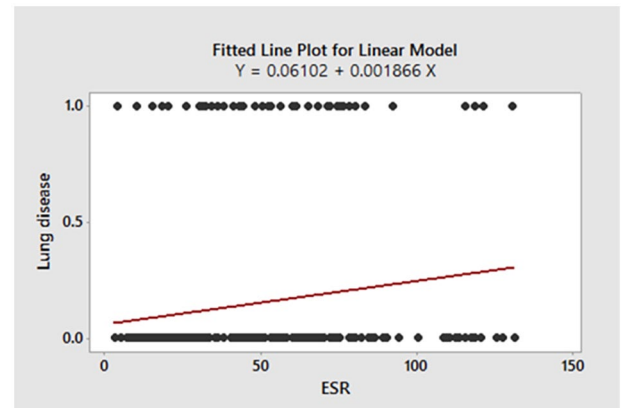
Disease severity categorized according to the DAS 28 depicts that most patients were in the moderately severe disease group (Figure 1).

Logistic regression analysis was used in assessing association in following:

| VARIABLE       | CHI SQUARE VALUE | P VALUE ( $P < .05$ SIGNIFICANT) |
|----------------|------------------|----------------------------------|
| Duration of RA | 14.1334          | .0002                            |
| DAS 28         | 11.9127          | .0006                            |
| ESR            | 7.8860           | .005                             |



**Figure 1.** Graph showing association between DAS 28 and lung disease. A positive but weak correlation ( $r=.18$ ) exists between DAS 28 and lung disease and the association was significant at  $P < .05$ .



**Figure 2.** Graph showing association between ESR and lung disease with a positive weak correlation ( $r=.15$ ), with a significant association ( $P < .05$ ).

Mean ESR of the ILD group was 45.44 (95% CI, 73.58-17.30) There was a positive correlation between ESR and lung disease ( $r=.15$ ). (Figure 2).

Average BMI of the group was 22.67 kg (mostly underweight).

A total of 24 patients (6.25%) were past (15) or present (9) smokers with a median of 26 pack-years.

From the cohort, majority (75.78%) were of low income (<50 000 rupees per month = 327 US \$), and only 24.21% had an income >50 000 rupees per month. A total of 23 patients had a diagnosis of IHD, 78 patients were on treatment for hypertension, 20 patients had diabetes, 2 patients had a diagnosis of COPD and 16 were on treatment for bronchial asthma.

From the cohort, 90 patients were underweight (23.43%) while majority were in normal BMI range for Asians (47.39%) and 29.6% were overweight. The prevalence of lung disease in the normal BMI group was 8.3%, while that for underweight group was 3.38% and overweight group was 2.86%.

About 91 were not on methotrexate treatment, stopped either due to side effects or intolerance, and the rest of the cohorts were on it. A total of 16 patients were on treatment with Rituximab and 2 patients were on Tocilizumab for the rheumatoid arthritis.

## Discussion

The prevalence of pulmonary abnormalities detected in association with RA vary widely and is likely to depend on multiple factors, notably the stage in the disease patients are studied, the source of patient referral and parameters used to define disease.<sup>20</sup> Gabbay et al<sup>20</sup> has shown abnormalities in at least 1 examination parameter in 56%, with changes most commonly being present on bronchoalveolar lavage (BAL) (52%) and HRCT (33%) and less commonly on physiology (22%) and only 6% with chest X-ray which is the commonest screening method. From our examination the prevalence of lung disease detected at the unit with CXR and HRCT was 14.58%, while lung disease detected in early RA was 5.4%. This is in keeping

with the reported prevalence of RA-ILD which is between 4% and 50%.<sup>21-25</sup>

Smoking is a modifiable risk factor associated with the development of ILD in RA. Our study also shows that smoking is significantly associated with development of lung disease. Lee et al<sup>26</sup> has shown that smoking is associated with UIP pattern of ILD.

Although there was a significant association of ILD with erosions, Koduri et al<sup>27</sup> have reported no association of erosions with the development of ILD in RA.

Study showed RF positivity to be significantly associated with ILD. This is in keeping with the findings of Mori et al<sup>28</sup> Disease severity measured by DAS 28 and ESR are also predictors of development of ILD in RA.<sup>29</sup>

Level of disease activity can be interpreted as DAS 28 score <2.6 (remission),  $\geq 2.6$  and <3.2 (low),  $\geq 3.2$  and <5.1 (moderate), and  $\geq 5.1$  (high,) disease activity.<sup>30</sup> Mean DAS 28 score of the study was  $4.58 \pm 1.09$  (95% CI, 3.48-5.68), falling into moderate disease activity group. Chen et al<sup>31</sup> has shown significant association with RA-ILD and the high titer of RF and DAS 28 scores. This was again confirmed by the current study showing a significant association between ESR, DAS 28, and ILD in RA.<sup>32</sup>

In this study the sex difference was not statistically significant as a cause for ILD in RA. In contrast, Weyand et al<sup>33</sup> has shown ILD to be more common in males compared to females whereas some studies have failed to show any male predominance.<sup>34</sup> Female to male ratio with rheumatoid arthritis was 7:1 and that of ILD group was 9:2, although the previous documented sex ratio in RA was 3:1.<sup>35</sup> This increase in female numbers may be due to the fact that more females attend to clinics than male patients who are mostly estate workers who earn daily wages.

Study has shown no association with the BMI and rheumatoid lung disease. Previous studies have shown an obesity paradox—a reduction in mortality in RA with increased obesity. This was true for lung disease associated RA deaths.<sup>36</sup>

## Conclusion

In this retrospective study we have found a prevalence of ILD in RA to be 14.58% which was significantly associated with disease severity indices such as DAS 28, ESR, erosion, and RF. Hence, even asymptomatic patients with high disease severity indices should be screened for lung involvement during follow-up.

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## Availability of Data and Material

The datasets used and or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethical Approval

Ethical approval obtained from the Ethical committee of university of Peradeniya, Sri Lanka

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