ORIGINAL ARTICLE

# Predictors and radiological characteristics of rheumatoid arthritis-associated interstitial lung disease in a multi-ethnic Malaysian cohort

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**ABSTRACT**

**Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that is commonly associated with extra-articular manifestations. Pulmonary disease is frequently encountered, which causes serious morbidity and increases mortality. Among the pulmonary manifestations, interstitial lung disease (ILD) is the most common. We aimed to analyse the frequency and clinical characteristics of a cohort of patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD); describe the radiological features of ILD; identify predictive factors for developing ILD; and evaluate the impact of ILD on patient survival.**

**Materials and Methods: This retrospective study included all patients with RA who attended the rheumatology clinic of Kuala Lumpur Hospital from 2018 to 2021. RA-ILD was identified from high-resolution computed tomography (HRCT) thorax images evaluated by two thoracic radiologists. Descriptive and logistic regression analyses were conducted using SPSS version 26.0.**

**Results: Of the 732 patients with RA, 7.4% (54) had ILD. Univariate analysis identified Indian ethnicity, rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide antibody titre, and diabetes mellitus as risk factors for developing ILD. Multivariable logistic regression showed that RA-ILD was positively associated with female gender [Adjusted odds ratio (aOR)=3.40 (95% confidence interval (CI): 1.04, 11.17)], Indian ethnicity [aOR=2.03 (95% CI: 1.16, 3.57)], and positive RF [aOR=2.39 (95% CI: 1.18, 4.87)]. Nonspecific interstitial pneumonia (NSIP) was the predominant HRCT pattern. Majority of patients had limited disease (<20% of lung involvement) and good functional exercise capacity. There was significant improvement ($p<0.05$) in mean forced vital capacity (FVC) following treatment with immunosuppressive agents. No mortality occurred throughout the median follow-up period of 3.2 years.**

**Conclusion: RA patients of Indian ethnicity had an increased risk for developing ILD, suggesting that genetics play a crucial role. Other independent predictors were female gender and RF positivity. The pattern of HRCT thorax and extent of lung involvement influenced prognosis and survival of patients with RA-ILD.**

**KEYWORDS:**
*Predictors, rheumatoid arthritis, interstitial lung disease, high-resolution computed tomography, prognosis*

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that most frequently affects the joints. If left untreated, RA can lead to progressive joint damage leaving patients with severe functional disability and loss of physical independence. Extra-articular manifestations are not uncommon and were reported to occur in approximately 40% of RA patients.[1] These manifestations include pulmonary disease, vasculitis, rheumatoid nodules, eye conditions, and cardiovascular disease. Pulmonary disease has been described to be the most frequently encountered extra-articular manifestation. Presentations of pulmonary involvement in RA are diverse, comprising parenchymal lung disease, pleural disease, pulmonary vascular disease, and airway complications. Of the pulmonary manifestations, interstitial lung disease (ILD) is the most common.[1,2]

The reported prevalence of ILD among patients with RA is exceedingly variable, ranging from 2% to 61%.[3-8] This wide variation is largely attributed to study design, case definition, method of detection, and population diversity. Several studies have shown that only a minority of patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) are symptomatic, indicating that asymptomatic RA-ILD is more prevalent.[7-9] Studies have also described that ILD can precede the onset of RA or develop during the initial few years of RA.[7,10-12] The prevalence of RA-ILD has been reported to increase with longer duration of RA.[5,12]

To date, high-resolution computed tomography (HRCT) thorax is regarded as the most appropriate tool to diagnose ILD because it has been demonstrated to be a sensitive

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technique for evaluation and detection of ILD.[8,13] Studies have demonstrated good correlation between the radiographic pattern found on HRCT thorax and the histopathologic pattern found on surgical lung biopsy for idiopathic pulmonary fibrosis (IPF), thus obviating the need for lung biopsy.[14] Likewise, this correlation was also demonstrated in the diagnosis of usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) in patients with RA-ILD, albeit the sample sizes of these studies were small.[11,15]

The most common HRCT patterns in RA-ILD are reportedly UIP and NSIP, with UIP being the predominant pattern.[11,15] Less common patterns are organising pneumonia (OP), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and diffuse alveolar damage.

Cardiovascular disease has been found to be the leading cause of death among RA patients.[16] This was followed by respiratory diseases, in particular, ILD.[17] Survival in patients with RA-ILD was reportedly shortened compared to patients with RA alone.[4] In addition, patients with ILD have a greater risk for developing pulmonary hypertension, which adds to the degree of morbidity.

Even though ILD is a well-recognised complication of RA, its aetiology and pathogenesis remain unclear. Numerous studies have attempted to identify the risk factors for ILD, which, to date, have not been well ascertained given conflicting and inconsistent results. In addition, several treatment modalities, in particular, methotrexate and anti-TNF (tumour necrosis factor) inhibitors, have been reported to be associated with increased risk of RA-ILD.[18,19] Regrettably, an optimal therapeutic strategy for patients with RA-ILD remains to be determined.

Our objectives were to analyse the demographic and clinical characteristics of a cohort of multi-ethnic patients with RA-ILD; describe the patterns of ILD and extent of lung involvement from HRCT thorax; identify factors associated with an increased risk for developing ILD; and evaluate the impact of ILD on patient survival.

## MATERIALS AND METHODS

This retrospective study was conducted at the rheumatology clinic of Hospital Kuala Lumpur. Medical records of all patients with RA between January 2018 and June 2021 were systematically reviewed. All patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.[20] Patients diagnosed with RA-ILD were identified. Those who had incomplete medical records were excluded from the study. Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, and registration was done in accordance with the National Medical Research Register Malaysia (NMRR-19-3450-52128).

The following data were obtained: patient demographics, duration of RA, duration from onset of RA to the diagnosis of RA-ILD from HRCT thorax, and disease activity score with 28-joint counts (DAS28) for RA using C-reactive protein at the time when HRCT thorax was performed.[21] Clinical data included history of ever smoking, body mass index (BMI), hypertension, diabetes mellitus, dyslipidaemia, and coronary heart disease. Respiratory symptoms and signs included non-productive cough for at least one month, exertional dyspnoea, bibasilar fine inspiratory crepitations, modified Medical Research Council (mMRC) dyspnoea scale, and findings suggestive of pulmonary fibrosis on plain chest radiography.[22] Laboratory parameters included rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) titre.

Patients who had undergone HRCT thorax examination were scrutinised. Medical records showed that patients who had clinical indications for ILD were subjected to HRCT thorax. The indications included respiratory symptoms or signs suspicious of ILD. Scan images were retrieved and evaluated independently by two thoracic radiologists, and the final scan findings were determined by consensus. Scans that were interpreted as ILD were identified. Radiological patterns were determined based on recommendations of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society clinical practice guidelines.[23] HRCT patterns were categorised as UIP, NSIP, OP, combination of NSIP and OP (NSIP-OP), probable UIP, indeterminate for UIP, and non-idiopathic pulmonary fibrosis (non-IPF). Each lung was divided axially into three zones and scored for the percentage of lung involvement, from which an average was calculated. Based on the percentage of lung involved, disease extent was further defined as limited (<20% of lung involvement) and extensive (≥20% of lung involvement) disease.[24]

With regard to treatment for RA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) ever received prior to and after HRCT thorax were recorded. Drug treatment ever received for RA-ILD, including dosage and duration of therapy, was documented. Forced vital capacity (FVC) measurements at baseline and after treatment for ILD were obtained. FVC value was expressed as percentage of predicted.

*Statistical Analysis*

Categorical variables were presented as frequencies and percentages. Normally distributed variables were presented as mean and standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR).

Pearson Chi-Square test was used to analyse the significance of association between each variable and RA-ILD. Two-sided $p<0.05$ was considered statistically significant. A logistic regression model was used to produce a crude odds ratio (OR) as a measure of the associations between the development of RA-ILD and the independent variables. For the final model, a forward likelihood ratio variable selection method was used to identify significant variables. Only variables with p values of <0.25 were entered into the multivariable logistic regression model. The adjusted odds ratio (aOR), with the respective 95% confidence interval (CI), was then calculated. A p value of <0.05 was considered significant. The model fit was tested using the Hosmer–Lemeshow statistic, which was non-significant ($p>0.05$). Comparison of continuous variables was made using independent t-test for normally

distributed data; otherwise, Mann–Whitney U test was applied. Descriptive and logistic regression analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) software for Windows, Version 26.0.

## RESULTS

A total of 732 patients with RA were identified. Demographic and clinical characteristics of the whole cohort are shown in Table I. Six hundred and twenty-three (85.1%) patients were female. Female gender was predominant in both groups of RA patients with and without ILD. Mean age at onset of RA was 48.9 (SD 13.4) years and median duration of RA was 8 (IQR 8) years.

ILD was present in 7.4% (54/732) of RA patients. Among the various ethnic groups, the frequency of ILD was highest among patients of Indian ethnicity at 51.9% (28/54), followed by Malay (31.5%) and Chinese (14.8%). Forty-four (81.5%) patients with ILD had positive rheumatoid factor (RF) and 37 (71.2%) had positive ACPA. Median ACPA titre was 199 (IQR 565) IU/ml. Six (11.1%) patients had other associated connective tissue diseases: three (5.6%) had systemic lupus erythematosus, two (3.7%) had systemic sclerosis, and one (1.8%) had polymyositis. With regard to comorbidities, 24 (44.4%) had dyslipidaemia, 20 (37%) had hypertension, 19 (35.2%) had diabetes mellitus, and five (9.3%) had coronary heart disease. Mean body mass index (BMI) was 27.5 (SD 6.4) kg/m$^2$ (Table II).

Past or current smoking was uncommon among our cohort of RA patients, with a frequency of under 10%. Among the patients with ILD, only 3 (5.6%) patients were smokers, and they were all men. In terms of csDMARD therapy for treatment of RA, majority (80.2%) of the patients received methotrexate. The percentage of patients receiving methotrexate in the group with ILD and without ILD was significantly different ($p<0.001$), wherein methotrexate use was significantly lower in RA patients with ILD.

Table II summarises the clinical characteristics of patients with RA-ILD. Mean age at diagnosis of RA-ILD was 55.8 (SD 11.7) years. Median duration from onset of RA to the diagnosis of ILD was 3.5 (IQR 5.2) years. ILD was diagnosed in eight (14.8%) patients within the first year of onset of RA, another nine (16.7%) by the second year of disease, and a further nine (16.7%) by the third year. This indicated that ILD developed in the early phase of RA. Mean DAS28 score at the point of HRCT thorax was 3.32 (SD 1.25), which was classified as moderate disease activity.

Median follow-up period after diagnosis of RA-ILD was 3.2 (IQR 3.8) years, with the longest duration of follow-up at 12.9 years. No mortality occurred throughout the follow-up period.

In terms of respiratory symptoms among the 54 patients with ILD, 15 (27.8%) experienced non-productive cough and 14 (25.9%) had exertional dyspnoea. Bibasilar fine inspiratory crepitations were detected in 48 (88.9%) patients, and 16 (29.6%) patients had findings suggestive of pulmonary fibrosis on chest radiographs. None of the patients developed pulmonary hypertension.

With regard to HRCT pattern, NSIP was the most frequently observed ILD pattern, at 44.5% (24/54) (Table III). This was followed by probable UIP at 18.5% (10/54), UIP in 11.1% (6/54), NSIP-OP in 9.3% (5/54), and OP in 9.3% (5/54). In terms of the extent of lung involvement, majority (88.9%) of patients had limited disease (<20% lung involvement). Baseline FVC was 63.3% (SD 13.4) predicted and 54.6% (SD 15.6) predicted in the groups classified as limited disease and extensive disease, respectively. There was no statistically significant difference in baseline FVC between patients with varying disease extent.

Baseline mMRC dyspnoea scale upon the diagnosis of ILD showed that a high proportion of patients (42/49, 85.8%) had scores of 0 and 1 (Table II). Five patients were not assessed because of significant arthritis involving the lower limbs. Baseline FVC was available for 45 (83.3%) patients with ILD. All of them showed a restrictive ventilatory defect. Mean baseline value of FVC was 62.4% (SD 13.8) predicted.

Thirty (55.6%) patients received treatment for ILD, of whom 27 received prednisolone alone, two received combination therapy with prednisolone and azathioprine, and one received mycophenolate mofetil. One of the two patients who received combination therapy had concomitant polymyositis; the patient who received mycophenolate mofetil had coexisting systemic sclerosis. Mean maximal dosage of prednisolone was 33.4 mg (SD 15.6) daily, with doses ranging from 15 mg to 75 mg daily. Median duration of treatment with prednisolone was 16 (IQR 13) weeks. Among the 29 patients who received prednisolone therapy, 16 had NSIP, four had NSIP-OP, four had OP, three had probable UIP, and two had UIP. The lone patient who received mycophenolate mofetil had NSIP pattern.

Baseline FVC was available in 26 of the 30 patients who received treatment for ILD. Mean baseline FVC value was 58.1% (SD 14.0) predicted. Nineteen patients had FVC measured pre- and post-treatment. Statistical analysis showed a significant improvement in mean FVC after treatment for ILD ($p<0.05$), whereby mean FVC pre-treatment was 56.4% (SD 14.4) predicted and mean FVC post-treatment was 61.6% (13.4) predicted.

*Predictive Factors for RA-ILD*

Table IV depicts the univariate and multivariable logistic regression analyses taken to examine risk factors associated with the development of RA-ILD. In univariate analyses, Indian ethnicity, RF positivity, higher titres of ACPA, and diabetes mellitus were associated with the development of RA-ILD. Multivariable analysis identified female gender, Indian ethnicity, and RF positivity as independent risk factors for developing ILD. Women had a 3.4-fold greater risk for RA-ILD [aOR=3.4 (95% CI: 1.04, 11.17)] compared to men. RA patients of Indian ethnicity had a two-fold increased risk compared to other ethnic groups [aOR=2.03 (95% CI: 1.16, 3.57)], and those with RF positivity were 2.39 times more likely to be associated with RA-ILD [aOR:2.39 (95% CI:1.18, 4.87)].

**Table I: Demographic and clinical characteristics of a multi-ethnic cohort of 732 patients with RA**

| Variable | All patients with RA (n=732) | RA without ILD (n=678) | RA with ILD (n=54) | p value |
|---|---|---|---|---|
| Gender, n (%) | | | | 0.045* |
| Male | 109 (14.9) | 106 (15.6) | 3 (5.6) | |
| Female | 623 (85.1) | 572 (84.4) | 51 (94.4) | |
| Ethnicity, n (%) | | | | 0.062 |
| Malay | 317 (43.3) | 300 (44.2) | 17 (31.5) | |
| Chinese | 147 (20.1) | 139 (20.5) | 8 (14.8) | |
| Indian | 259 (35.4) | 231 (34.1) | 28 (51.9) | |
| Others | 9 (1.2) | 8 (1.2) | 1 (1.8) | 0.062 |
| Mean age (SD), years | 58.1 (13.4) | 58.0 (13.5) | 59.6 (11.9) | 0.417 |
| Mean age at onset of RA (SD), years | 48.9 (13.4) | 48.8 (13.4) | 50.3 (13.0) | 0.427 |
| Median duration of RA (IQR), years | 8 (8) | 8 (8) | 7 (7) | 0.896 |
| Rheumatoid factor positivity, n (%) | 478 (66.8) (n=716) | 434 (65.6) | 44 (81.5) | 0.017* |
| ACPA positivity, n (%) | 433 (66.9) (n=647) | 396 (66.6) (n=595) | 37 (71.2) (n=52) | 0.499 |
| Median ACPA titre (IQR), U/ml | 95 (338) | 87 (338) | 199 (565) | 0.004* |
| **Comorbidities, n (%)** | | | | |
| Smoking (ever) | 65 (8.9) | 62 (9.1) | 3 (5.6) | 0.465 |
| Hypertension | 268 (36.6) | 248 (36.6) | 20 (37.0) | 0.946 |
| Diabetes mellitus | 169 (23.1) | 150 (22.1) | 19 (35.2) | 0.028* |
| Dyslipidaemia | 270 (36.9) | 246 (36.3) | 24 (44.4) | 0.232 |
| Coronary heart disease | 51 (7.0) | 46 (6.8) | 5 (9.3) | 0.414 |
| **csDMARDs, n (%)** | | | | |
| Methotrexate | 587 (80.2) | 555 (81.9) | 32 (59.3) | 0.000* |
| Sulfasalazine | 408 (55.7) | 378 (55.8) | 30 (55.6) | 0.978 |
| Leflunomide | 195 (26.6) | 185 (27.3) | 10 (18.5) | 0.161 |
| Hydroxychloroquine | 131 (17.9) | 123 (18.1) | 8 (14.8) | 0.539 |

*denotes significant p value of <0.05.
RA: rheumatoid arthritis; ILD: interstitial lung disease; SD: standard deviation; IQR: interquartile range; ACPA: anti-cyclic citrullinated peptide antibody; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs

## DISCUSSION

Our data showed that the frequency of ILD in 732 multi-ethnic patients with RA was 7.4%, almost similar to that reported by Bongartz et al. where the incidence was 7.7% among 582 patients with RA.[4] We wish to highlight that the medical records of our RA patients showed that HRCT thorax was not ordered at random but directed at patients who exhibited pulmonary symptoms or clinical signs suggestive of ILD. Therefore, asymptomatic patients with ILD were inevitably precluded. As a comparison, studies where all RA patients were subjected to routine HRCT thorax showed a higher frequency of RA-ILD. Yin et al. reported 24.9% of patients with ILD, Gabbay et al. 33%, Zhang et al. 43.1%, and Chen et al. 61%.[5-8] A significant proportion of patients with RA-ILD were asymptomatic as demonstrated by Gabbay et al. (44%) and Chen et al. (55%).[7,8]

It has been widely reported that male gender, older age, smoking, and RF and ACPA positivity indicate greater risk for the development of ILD.[4,5,24,25] In our study, multivariate analyses identified female gender, Indian ethnicity, and RF positivity as predictive factors for developing ILD. The female to male ratio in our patients with RA was approximately 6:1, while the ratio for patients with RA-ILD was 17:1

Given our multi-ethnic population in Malaysia, our data revealed that the risk for developing ILD was significantly higher in patients of Indian ethnicity (p<0.05). Indian patients constituted 51.9% of the total number of patients with RA-ILD, albeit the proportion of Indian patients with RA was 35.4%. This finding is not consistent with the demographic of Malaysia wherein individuals of Indian ethnicity constitute a mere 6.8% of the population. For the information of our readers, the predominant ethnic group in Malaysia is Malay, comprising 69.6% of the population, followed by Chinese at 22.6%.[26] Of note, an earlier research conducted in Malaysia by Shahrir et al. identified Indian as the predominant (54.5%) ethnic group among patients with RA.[27] Interestingly, a research conducted in multi-ethnic South Africa also found that the majority of their patients with RA-ILD were of Indian ethnicity, comprising 72.1%, when in fact the same ethnic group constituted only 7.9% of the entire population.[28] These observations strongly suggest that ethnic Indians are more susceptible to developing RA as well as RA-ILD, indicating the impact of genetic factors.

RF and ACPA are biomarkers that are useful in the diagnosis of RA, and they have also been shown to be associated with more aggressive disease.[37] Nonetheless, the association between seropositivity for RF and ACPA in relation to RA-ILD remains controversial. Chen et al. and Ghammo et al.[8,28] failed to show any association between RF and ACPA positivity with RA-ILD, while Yin et al., Kelly et al., and Zhu et al. managed to demonstrate statistically significant positive correlation.[5,24,30] In our study, the presence of RF, but not ACPA, was strongly associated with the development of

**Table II: Clinical characteristics of 54 patients with RA-ILD**

| Characteristics | Number (%) | Mean (SD) | Median (IQR) | Range |
|---|---|---|---|---|
| Age at diagnosis of RA-ILD, years | | 55.8 (11.7) | | 26.4-80.8 |
| Duration from onset of RA to diagnosis of RA-ILD, years | | | 3.5 (5.2) | 0.17-30.5 |
| Duration of follow-up after dx of RA-ILD, years | | | 3.2 (3.8) | 0.25-12.9 |
| DAS28 at the time of HRCT thorax (n=50) | | 3.32 (1.25) | | |
| BMI, kg/m$^2$ (n=53) | | 27.5 (6.4) | | |
| **Respiratory symptoms and signs** | | | | |
| Non-productive cough | 15 (27.8) | | | |
| Exertional dyspnoea | 14 (25.9) | | | |
| Bibasilar fine crepitations | 48 (88.9) | | | |
| Features of pulmonary fibrosis on chest radiograph | 16 (29.6) | | | |
| **mMRC dyspnoea scale (n=49)** | | | | |
| Score 0 | 24 (49.0) | | | |
| Score 1 | 18 (36.8) | | | |
| Score 2 | 6 (12.2) | | | |
| Score 3 | 1 (2.0) | | | |
| Baseline FVC, % predicted (n=45) | | 62.4 (13.8) | | |
| **Treatment for ILD** | | | | |
| Prednisolone | 29 (53.7) | | | |
| - Maximal dose, mg/day | | 33.4 (15.6) | | 10-75 |
| - Duration of treatment, weeks | | | 16 (13) | 10-57 |
| Azathioprine | 2 (3.7) | | | |
| - Maximal dose, mg/day | | 150 | | |
| Mycophenolate mofetil | 1 (1.9) | | | |
| - Maximal dose, g/day | | 2 | | |
| Survival status | | | | |
| Alive | 54 (100) | | | |
| Not alive | 0 (0) | | | |

Where n is not stated, it indicates 54 subjects.
HRCT: high-resolution computed tomography; SD: standard deviation; IQR: interquartile range; DAS 28: disease activity score for 28 joints; BMI: body mass index; mMRC: modified Medical Research Council; FVC: forced vital capacity

**Table III: Radiological patterns of ILD and pulmonary function in patients with RA-ILD**

| | | HRCT thorax | |
|---|---|---|---|
| **HRCT thorax** | **Patients with RA-ILD, number (%) n=54** | **Extent of lung involvement, number (%)** | |
| | | **Limited disease (<20%), n=48** | **Extensive disease (≥20%), n=6** |
| UIP | 6 (11.1) | 4 | 2 |
| Probable UIP | 10 (18.5) | 10 | 0 |
| Indeterminate for UIP | 2 (3.7) | 2 | 0 |
| NSIP | 24 (44.4) | 21 | 3 |
| NSIP-OP | 5 (9.3) | 5 | 0 |
| OP | 5 (9.3) | 4 | 1 |
| Non-IPF | 2 (3.7) | 2 | 0 |
| **Pulmonary function** | **Limited disease** | **Extensive disease** | **p value** |
| FVC (SD), % predicted | 63.3 (13.4) | 54.6 (15.6) | 0.184 |

HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity

**Table IV: Unadjusted and adjusted odds ratio of clinical associations for development of RA-ILD**

| | Unadjusted OR | | Adjusted OR (aOR) | |
|---|---|---|---|---|
| | OR (95% CI) | p value | aOR (95% CI) | p value |
| Gender | | | | |
| Female | 3.150 (0.965, 10.280) | 0.057 | 3.404 (1.037, 11.169) | 0.043* |
| Ethnicity | | | | |
| Indian | 2.084 (1.194, 3.637) | 0.010* | 2.032 (1.158, 3.565) | 0.013* |
| Age | 1.009 (0.988, 1.031) | 0.416 | - | - |
| Age at onset of RA | 1.009 (0.988, 1.030) | 0.426 | - | - |
| Duration of RA | 0.995 (0.958, 1.034) | 0.802 | - | - |
| RF | 2.312 (1.142, 4.679) | 0.020* | 2.394 (1.177, 4.867) | 0.016* |
| ACPA | 1.240 (0.664, 2.313) | 0.500 | - | - |
| ACPA titre | 1.001 (1.000, 1.003) | 0.010* | 1.001 (1.000, 1.002) | 0.181 |
| Smoking, ever | 0.584 (0.177, 1.927) | 0.378 | - | - |
| Hypertension | 1.020 (0.574, 1.811) | 0.946 | - | - |
| Diabetes mellitus | 1.911 (1.062, 3.438) | 0.031* | 1.653 (0.814, 3.358) | 0.165 |
| Dyslipidaemia | 1.405 (0.803, 2.457) | 0.233 | 1.233 (0.635, 2.395) | 0.537 |
| Coronary heart disease | 1.402 (0.533, 3.689) | 0.494 | | |

*denotes significant p value of <0.05.
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibody

ILD. On univariate analysis, higher titres of ACPA showed a significant correlation with ILD compared to patients without ILD (199 U/ml in ILD group vs. 87 U/ml in non-ILD group, p<0.01). However, the significance of ACPA titre appeared less evident on multivariable analysis. This discrepancy may be attributed to the fact that data on ACPA were unavailable in 11.6% of patients. High titres of ACPA have been reported as risk factors for ILD from multivariate analysis.[25,31] Given these evidences, it is conceivable that higher levels of ACPA may well be predictive for the development of RA-ILD.

Several authors have found that older age and older age at onset of RA were significantly associated with the development of ILD.[4-6,8,12,25,31] Nonetheless, our cohort failed to demonstrate any correlation in terms of age of patients or age at onset of RA. In addition, there was no significant relationship between duration of RA with occurrence of RA-ILD.

The median duration from the onset of RA to the diagnosis of RA-ILD was 3.5 years. Of the 54 patients with RA-ILD, 26 (48.1%) patients were detected to have ILD within 3 years from the onset of RA, and 36 (66.7%) had ILD by 5 years. In our study, ILD presented early in the course of RA, consistent with findings in previous studies.[7,9,12]

We also examined the presence of comorbidities in relation to RA-ILD. Among the various comorbidities, only diabetes mellitus showed a significant association with RA-ILD on univariate analysis. Hypertension, dyslipidaemia, and coronary heart disease failed to demonstrate positive correlation. Ehrlich et al. have reported that patients with diabetes mellitus were at increased risk for pulmonary fibrosis, even though the exact mechanism and causal relationship have yet to be established.[32]

Smoking has been identified as an important risk factor for the development of RA in earlier epidemiological studies.[33,34] Among our patients, past or active smoking did not show significant association with RA-ILD. The correlation between smoking and risk of ILD is still debatable. Several studies demonstrated a positive association, while others did not.[5,6,9,12,25,35] Interestingly, Kronzer et al. found that among patients with RA who smoked, heavier smokers had a higher risk of developing ILD.[35] Of note, the prevalence of smoking was low among our patients, and this may have an impact on the analysis of this variable as a predictive factor for the development of ILD.

Among our RA patients who had clinical indications for HRCT thorax, findings of bibasal fine crepitations were more frequent than the presence of respiratory symptoms. This reiterated the fact that patients with RA-ILD are generally asymptomatic, unlike patients with IPF or other connective tissue diseases.[7-9] Therefore, we would like to emphasise to physicians that careful physical examination of RA patients is crucial. A greater proportion (85.7%) of our patients with RA-ILD had mMRC dyspnoea scale of 0 and 1, indicating mild disease or clinically insignificant disease. This was corroborated by the fact that 88.9% (48/54) of them had limited disease (<20% of lung involvement).

It is widely recognised that UIP is the predominant radiological pattern of ILD in patients with RA.[11,15,24,31,36] Nonetheless, this is in contrast to our data, which demonstrated that NSIP was the most frequent pattern, accounting for almost 45% of patients. Interestingly, the frequency of UIP pattern among our patients was considerably lower, at 11.1%. Our findings confirmed the observations described by Zhang et al.[6] Several authors have reported that patients with UIP pattern had poorer prognosis with worse survival when compared to patients with non-UIP patterns.[10,24,37,38]

In our study, no mortality occurred throughout the median follow-up period of 3.2 years (ranging from 0.25 to 12.9 years) after the diagnosis of RA-ILD was established. This could be explained by the low frequency of UIP among our patients, the higher proportion of patients who had limited disease on HRCT thorax, and a favourable response to immunosuppressive agents in the treatment for ILD. Data from a multi-centre study conducted by Kelly et al. found that

patients with extensive disease had an increased risk of mortality.[24] With regard to treatment for ILD, Lee et al. showed that patients with NSIP generally responded well to corticosteroids, thus improving survival.[39] To date, current recommendations on the optimal therapeutic regime for RA-ILD remains to be determined.

For the interest of our readers, mycophenolate mofetil (MMF) was prescribed to the patient with RA-ILD who had coexisting systemic sclerosis.

Methotrexate is generally considered as the first-line DMARD agent for treatment of RA. The present study confirmed that majority of our RA patients received methotrexate. However, the proportion of patients receiving methotrexate was significantly lower ($p<0.05$) in the ILD group compared to the group without ILD. It is conceivable that the reluctance to prescribe methotrexate in patients with RA-ILD stemmed from reported occurrence of methotrexate-induced lung injury in patients with RA.[18] Nevertheless, a recent systematic literature review by Fragoulis et al. reported a lack of association between methotrexate and development of ILD in RA patients.[40] This evidence should prompt us to re-consider a change in our therapeutic approach with regard to the use of methotrexate in patients with RA-ILD. Even though it is not advisable to commence methotrexate in RA patients with compromised respiratory reserve, the use of methotrexate is not an absolute contraindication in patients with pre-existing ILD who have reasonable respiratory function.

Several limitations in this study were identified. This is a retrospective, single-centre study; involvement of multiple centres may provide more meaningful results. The missing data on ACPA titres may have contributed to the negative predictive effect of ACPA titre for ILD in multivariate analysis, when in fact there was positive association on univariate analysis. The short duration of follow-up after the diagnosis of ILD was established may not have reflected the actual mortality rate associated with RA-ILD. A study with longer follow-up may be helpful in determining survival in patients with RA-ILD.

Nonetheless, there are several strong points in our study. The large sample size of RA patients allowed us to evaluate the frequency of RA-ILD more effectively. Multiple clinical and laboratory variables were analysed to determine the predictive factors for developing ILD. We categorised the disease extent to further understand the characteristics of ILD in our RA patients.

In conclusion, female gender, Indian ethnicity, and RF positivity were independent predictors for the development of RA-ILD. Higher ACPA titres and presence of diabetes mellitus were also predictive of ILD, albeit in univariate analysis. NSIP was the predominant radiological pattern on HRCT thorax, with the majority of patients having limited disease. Even though this study was not designed to compare with ILD in IPF or other connective tissue diseases, RA-ILD in our cohort appeared to be less severe with better prognosis. Finally, there remains a pressing need for collaboration in randomised controlled trials in order to generate robust evidence to determine recommendations and guidance on the optimal therapeutic approach for patients with RA-ILD.

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## CONFLICTS OF INTEREST / COMPETING INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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