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

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INTRODUCTION

Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis (RA) and is associated with significant morbidity and mortality. Previous studies have shown variability in predictive factors for RA-associated ILD (RA-ILD). High-resolution computed tomography (HRCT) thorax is regarded as the modality of choice in the diagnosis and prognostic evaluation of ILD. Among the HRCT patterns in RA-ILD, usual interstitial pneumonia (UIP) has been widely reported as the predominant radiological pattern, and is associated with poorer prognosis and worse survival. To date, recommendations on the optimal therapeutic regime for RA-ILD remains to be determined. The objectives of our study are to analyse the frequency and clinical characteristics of patients with RA-ILD, to describe the HRCT patterns of ILD and the extent of lung involvement, to evaluate the predictive factors for developing ILD and to analyse the survival of patients with RA-ILD.

METHODOLOGY

This retrospective study included all patients with RA from the rheumatology clinic of Kuala Lumpur Hospital from 2018 to 2021. All patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. Patients who had undergone HRCT thorax were examined. Diagnosis of RA-ILD and evaluation of HRCT patterns and percentage of lung involvement were made independently by two thoracic radiologists. Disease extent was defined as limited (<20% of lung involvement) and extensive (≥20% of lung involvement). Potential predictors of RA-ILD were analysed by logistic regression analyses. Only variables with p<0.25 were entered into multivariable logistic regression model. Significance was set at p<0.05. Statistical analyses were conducted using SPSS version 26.0.

RESULTS

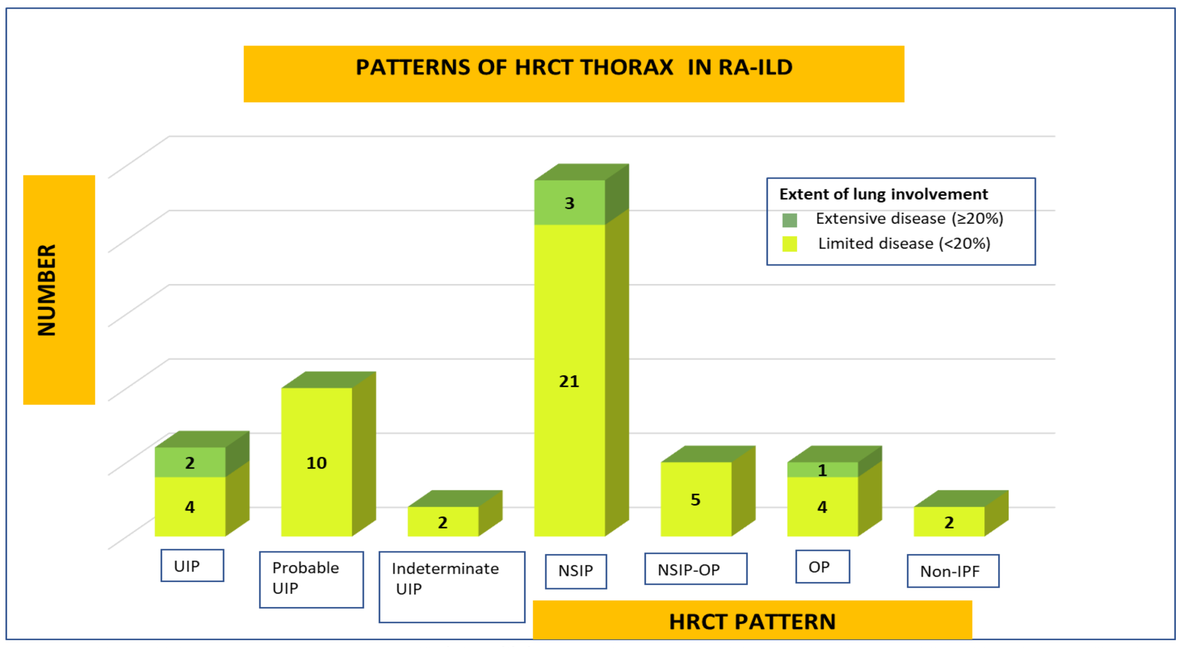
Of the 732 patients with RA, 54 (7.4%) had RA-ILD. Table 1 illustrates the demographic and clinical characteristics of the whole cohort.

Variable	RA without ILD (n=678)	RA with ILD (n=54)	p value
Gender, n (%)			0.045*
Male	106 (15.6)	3 (5.6)	
Female	572 (84.4)	51 (94.4)	
Ethnicity, n (%)			0.062
Malay	300 (44.2)	17 (31.5)	
Chinese	139 (20.5)	8 (14.8)	
Indian	231 (34.1)	28 (51.9)	
Others	8 (1.2)	1 (1.8)	
Mean age (SD), years	58.0 (13.5)	59.6 (11.9)	0.417
Mean age at onset of RA (SD), years	48.8 (13.4)	50.3 (13.0)	0.427
Median duration of RA (IQR), years	8 (8)	7 (7)	0.896
Rheumatoid factor positivity, n (%)	434 (65.6)	44 (81.5)	0.017*
ACPA positivity, n (%)	396 (66.6) (n=595)	37 (71.2) (n=52)	0.499
Median ACPA titre (IQR), U/ml	87 (338)	199 (565)	0.004*
Comorbidities, n (%)			
Smoking (ever)	62 (9.1)	3 (5.6)	0.465
Hypertension	248 (36.6)	20 (37.0)	0.946
Diabetes mellitus	150 (22.1)	19 (35.2)	0.028*
Dyslipidaemia	246 (36.3)	24 (44.4)	0.232
Coronary heart disease	46 (6.8)	5 (9.3)	0.414

*denotes significant p value of < 0.05. SD: standard deviation; IQR: interquartile range; ACPA: anti-cyclic citrullinated peptide antibody

Table 1. Baseline characteristics of patients with RA and RA-ILD

Nonspecific interstitial pneumonia (NSIP) was the predominant HRCT pattern (44.4%). The majority of patients had limited disease and good functional exercise capacity (Figure 1). The median duration from the onset of RA to the diagnosis of RA-ILD was 3.5 years (range from 0.25 to 12.9 years).



UIP – usual interstitial pneumonia; NSIP – nonspecific interstitial pneumonia; OP – organising pneumonia; IPF – idiopathic pulmonary fibrosis

Figure 1. Patterns of HRCT thorax in patients with RA-ILD

Thirty patients with RA-ILD were treated with immunosuppressive agents, of which prednisolone was the most frequently used drug (29/30 patients). There was significant improvement in mean forced vital capacity (FVC) after treatment (p<0.05). There were no mortalities throughout the follow-up period after the diagnosis of ILD was established [median of 3.2 (IQR 3.8) years; range of 0.25-12.9 years].

Univariate analysis identified Indian ethnicity, rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide antibody (ACPA) titre and diabetes mellitus as risk factors for developing ILD. Multivariable logistic regression showed that RA-ILD was positively associated with female gender, Indian ethnicity and positive RF (Table 2).

Variable	Unadjusted OR OR (95% CI)	p value	Adjusted OR (aOR) 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	-	-
Rheumatoid factor	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; ACPA: anti-cyclic citrullinated peptide antibody

Table 2. Predictors for development of RA-ILD

DISCUSSION

The frequency of RA-ILD varied widely in published studies (ranging from 2% to 61%), largely attributed to differences in study design, case definition and method of detection of ILD. It has been widely reported that male gender, older age at onset of RA, smoking, RF positivity and ACPA positivity are risk factors for the development of RA-ILD. In contrast, our study showed that female gender was a predictor for developing ILD (p<0.05). The female to male ratio in our patients with RA was approximately 6:1 while the ratio in patients with RA-ILD was 17:1.

Our data revealed that the risk for developing ILD was significantly higher in patients of Indian ethnicity (p<0.05). Indian patients constituted the greatest proportion of patients with RA-ILD at 51.9%, although the proportion of Indians among patients with RA was 35.4%. Research conducted in multi-ethnic South Africa also found that the majority of their patients with RA-ILD were of Indian ethnicity (72.1%). This suggests that ethnic Indians with RA are more susceptible to ILD, indicating that genetics play a role in the pathogenesis of disease.

In our study, the presence of RF, but not ACPA, was strongly associated with the development of ILD. On univariate analysis, higher titres of ACPA showed a significant correlation with RA-ILD compared to patients without ILD (199 U/ml in ILD group vs 87 U/ml in non-ILD group, p<0.01). Nonetheless, the association between RF and ACPA positivity in relation to RA-ILD remains controversial as demonstrated in several studies.

In contrast to previous studies, our study did not identify any significant associations between older age at onset of RA and smoking with the risk of developing ILD.

RA-ILD in our cohort appeared to be less severe and had better prognosis. No mortality occurred throughout the follow-up period. This could be explained by the low frequency of UIP among our patients, the higher proportion of patients who had limited disease and a favourable response to immunosuppressive agents in the treatment for ILD. Of note, UIP pattern and extensive disease have been shown in previous studies to be associated with poorer prognosis and worse survival. The predominant radiological pattern in our cohort was NSIP, which has been shown to respond well to corticosteroids.

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.
- RA-ILD in our cohort appeared to be less severe and has a better prognosis.
- NSIP was the predominant radiological pattern on HRCT thorax, with the majority of patients having limited disease.
- Therefore, knowledge of predictors and radiological characteristics of RA-ILD may be useful for prognostication and serve as guidance to recommendations on the optimal therapeutic approach for RA-ILD.

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