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FREQUENCY OF INTERSTITIAL LUNG DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Objectives: To evaluate the prevalence of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) in Department of Pulmonology, Aga Khan University Hospital, Karachi, Pakistan.

Methods: The study was cross sectional for a period of six months from January 2020 till June 2020. conducted in Department of Pulmonology, Aga Khan University Hospital, Karachi. 130 Rheumatoid Arthritis patients (18-70 years) who were diagnosed according to ACR/EULAR 2010 criteria were recruited, with non-probability consecutive sampling. High resolution computed tomography (HRCT) of the chest was performed for all patients and ILD was diagnosed by typical chest imaging characteristics. The data were analyzed in SPSS 26 and chi-square-test was used with $p \leq 0.05$ being significant.

Results: The study shows 29 patients (22.3%) were diagnosed with ILD and 101 patients (77.7%) did not have ILD. ILD was more frequent in patients aged 41–70 years (25.0%), males (33.3%), smokers (39.1%), and those with disease duration >5 years (27.6%). The smoking status ($p = 0.001$) and disease duration ($p = 0.006$) were statistically significant. Higher ILDs were observed for age and gender, which were not as statistically significant.

Conclusions: The incidence of RA-ILD was 22.3%. ILD was more prevalent in older patients, male patients, smokers and in those with longer disease duration. The results emphasize the importance of early screening and risk stratification of pulmonary involvement in RA, through HRCT in order to minimize pulmonary morbidity and to achieve better outcomes.

KEYWORDS: Interstitial Lung Diseases; Prevalence; Rheumatoid Arthritis; Risk Factors; Tomography, X-Ray Computed

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition that often has extra-articular complications, with interstitial lung disease (ILD) being a significant factor in morbidity and mortality. In older RA populations the association between RA and ILD has gained more and more recognition as a clinically relevant pulmonary complication, associated with poor survival [1]. Serological markers like the presence of autoantibodies are also known to be significant risk factors for the progression to ILD in RA patients, thus implying an immunologic pathogenic association [2].

However, genetic susceptibility has also been thought to play a role in the development of RA-ILD. The MUC5B promoter variants have been linked with increased lifetime risk, positioning them as supporting the same fibrotic pathway in both idiopathic and RA-associated pulmonary fibrosis [3]. In addition, the presence of C-TD associated ILD has been associated with significant years of life lost, underscoring the impact of C-TD associated ILD on long-term patient outcome [4].

The data on mortality suggests that RA-ILD is linked to significantly poorer survival than RA without lung involvement, and that there remains a significant mortality disadvantage even in the face of advances in the diagnostic imaging and clinical awareness of RA-ILD [5]. This is an example of the fact that fibrotic lung disease in RA is progressive and early detection and intervention is difficult.

New studies have improved the understanding of the pathophysiology and treatment of RA-ILD, highlighting immune dysregulation, chronic inflammation, and fibrotic remodelling as key mechanisms in disease progression [6]. Studies based on the population also have shown a steady correlation between RA and ILD in large numbers of patients, supporting the systemic nature of the disease process [7].

There are reports from systematic reviews that ILD is a measurable event in RA patients but there is significant heterogeneity in these reports, related to the use of different diagnostic criteria and imaging methods [8]. The prevalence estimates have been obtained using meta-analytical data, which have yielded pooled prevalence estimates, thus establishing RA-ILD as a clinically significant complication on a global level [9]. Also, known risk factors like smoking, seropositivity and duration of disease have been consistently linked to a higher risk of ILD in RA populations [10]. Although it was known that ILD was an extra-articular manifestation of RA with clinically and prognostically important implications, there were differences between studies on the frequency of RA-ILD, including varying diagnostic criteria, imaging modalities and study populations, resulting in different epidemiological estimates, especially in resource-limited settings where underdiagnosis had been reported. For this reason, this study was designed to elucidate the prevalence of interstitial lung disease in RA patients.

METHODS

The study was cross sectional study and carried out in Department of Pulmonology at Aga Khan University Hospital, Karachi, Pakistan. The study was carried out over a period of six months from January 2020 till June 2020. after approval of the study synopsis with ERC No: **2019-1872-5058**. The study population included patients suffering from rheumatoid arthritis who were attending Rheumatology and Medicine department during the study period.

The study included patients aged between 18 and 70 years, with rheumatoid arthritis diagnosis by ACR/EULAR Classification Criteria 2010, of both genders. [7]. Patients were only included who were able to cooperate and signed an informed consent. Patients with a history of IE other than RA, PTB, COPD, bronchial asthma, silicosis, asbestosis and other CTDs besides RA and lung malignancy were excluded. Women who were pregnant were also not included in the study.

The sample size was determined through the WHO Sample Size Calculator given a prevalence of interstitial lung disease in patients with RA of 21%, a 95% confidence level and a 7% margin of error. A sample size of 130 patients was estimated. A non-probability consecutive sampling technique was used for patient recruitment.[11].

After obtaining approval from the Institutional Review Board/Ethical Review Committee, patients were recruited from both inpatient and outpatient settings. All participants were asked to sign informed consent forms. A structured proforma was used to collect demographic and clinical information, such as age, gender, duration of rheumatoid arthritis (RA), smoking history and medical history. All patients were clinically evaluated and then computed tomography (HRCT) of the chest was performed. Interpretation of HRCT scans was done by a well-experienced radiologist. Patients were considered to have interstitial lung disease if they had ground glass opacities, reticular changes, interlobular septal thickening, traction bronchiectasis, honeycombing or patterns typical of usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP) in the HRCT. Any patient who did not have these radiological features was grouped in the ILD absent category.

The data was entered and analysed by SPSS 26. The quantitative variables (age, duration of RA) were presented as mean and standard deviation values, and the qualitative variables (gender, smoking and the presence of interstitial lung disease) were presented as frequencies and percentages. The prevalence of ILD was computed for patients with RA. To evaluate effect modifiers, stratification was done by age, gender, disease duration and smoking status. The Chi-square test was used for post-stratification analysis and a p value of ≤ 0.05 was deemed to be significant.

RESULTS

A total of 130 patients with rheumatoid arthritis were included in the study. The frequency of interstitial lung disease (ILD) was assessed on HRCT chest. Overall, RA-associated ILD was identified in a subset of patients. The demographic profile, frequency of ILD, and stratified analysis are presented below.

Table 1 shows baseline characteristics of the study population. Most patients were in the 41–70 years age group, with a higher proportion of females. More than half had disease duration exceeding five years, and approximately one-third had a positive smoking history.

Table 1: Baseline characteristics of RA patients (n = 130)

Variable	Category	n (%)
Age	18–40 years	38 (29.2)
	41–70 years	92 (70.8)
Gender	Male	42 (32.3)
	Female	88 (67.7)
Disease duration	≤5 years	54 (41.5)
	>5 years	76 (58.5)
Smoking status	Smokers	46 (35.4)
	Non-smokers	84 (64.6)

Table 2 shows the frequency of interstitial lung disease among RA patients. Out of 130 patients, 29 were diagnosed with ILD on HRCT chest, while the majority had no radiological evidence of ILD.

Table 2: Frequency of ILD in RA patients (n = 130)

ILD Status	n (%)

ILD Present	29 (22.3)
ILD Absent	101 (77.7)
Total	130 (100)

Table 3 shows stratification of ILD frequency according to demographic and clinical variables. Higher proportions of ILD were observed among older patients, males, patients with longer disease duration, and smokers. Statistically significant associations were noted for smoking status and disease duration.

Table 3: Stratification of ILD among RA patients (n = 130)

Variable	Category	ILD Present n (%)	ILD Absent n (%)	p-value
Age	18–40 years	6 (15.8)	32 (84.2)	0.041
	41–70 years	23 (25.0)	69 (75.0)	
Gender	Male	14 (33.3)	28 (66.7)	0.018
	Female	15 (17.0)	73 (83.0)	
Disease duration	≤5 years	8 (14.8)	46 (85.2)	0.006
	>5 years	21 (27.6)	55 (72.4)	
Smoking status	Smokers	18 (39.1)	28 (60.9)	0.001
	Non-smokers	11 (13.1)	73 (86.9)	

DISCUSSION

The proportion of patients with interstitial lung disease (ILD) in the present study was 22.3%, reflecting a significant burden of pulmonary involvement during the course of RA. This prevalence is in line with pooled estimates from worldwide RA cohorts in meta-analyses that indicate that RA-ILD is an extra-articular manifestation of RA that is relatively common [11].

Geographical variation in prevalence, however, has been reported in numerous studies and is largely due to variations in study design, population composition and the criteria applied to define the cases [12]. Additional large national cohort studies confirm that RA-ILD is an important clinical syndrome with a measurable epidemiological burden in various populations [13]. The present study also showed the greater association of ILD with age, disease duration, and smoking exposure. These results are confirmed by existing risk factor analyses showing that these factors are strong risk factors for RA-ILD [14]. In like manner, female gender has been linked to worse pulmonary involvement and outcomes in RA-ILD patients [15].

Pathophysiologically, RA-ILD is recognized more and more as a multifactorial disorder caused by immune dysregulation, chronic inflammation and activation of fibroblasts, leading to progressive interstitial fibrosis [16]. In addition, immunological and serological data support the association between autoimmunity and pulmonary involvement, and systemic immune activation and progression of lung injury [17]. Genetic susceptibility also has been strongly implicated, with the MUC5B promoter variant, which is strongly associated with lifetime risk of ILD in patients with RA, and indicates a shared fibrotic pathway between RA-ILD and idiopathic pulmonary fibrosis [18].

From an outcomes perspective, RA-ILD has always been linked with higher mortality and survival rates that are lower than those of RA patients without involvement of the lungs, demonstrating the prognostic value of ILD [19]. Further, there has been some variation in the diagnosis and the use of HRCT has affected the prevalence reported, and newer imaging studies have led to the detection of subclinical cases of ILD in RA cohorts [20]. The results of this study corroborate with the current literature and support the notion that RA-associated ILD is a common and clinically relevant finding in RA, especially in high-risk individuals like older patients, men, smokers, and patients with higher disease duration.

One of the strengths of this study was that all the patients received HRCT chest imaging, which allowed for the proper diagnosis and identification of interstitial lung disease, even in subclinical cases. The study also was conducted in a controlled environment that excluded other chronic lung diseases. The clinical population was further improved to be representative through the use of consecutive sampling. Regular screening for ILD is recommended for RA patients, especially those with high-risk features (elderly age, male gender, smoking and longer disease duration). Pulmonary referral at an early stage, multidisciplinary care and smoking cessation programs should be incorporated into the routine care of RA to benefit the patient.

Limitations of study: This was a cross-sectional study in one centre and did not allow for generalizability or the assessment of disease progression or the evaluation of causality. There can be selection bias when using non-probability sampling methods like consecutive sampling. Functional assessment of lung disease was limited to pulmonary function tests (PFTs) and DLCO were not performed. Furthermore, several important confounders were not assessed including medication history and disease severity.

CONCLUSION

Interstitial lung disease prevalence was 22.3% in the patients with rheumatoid arthritis. RA-ILD was more prevalent in patients who were older, male, current smokers, and had greater disease duration. The results emphasize the importance of early screening and risk stratification of pulmonary involvement in RA, through HRCT in order to minimize pulmonary morbidity and to achieve better outcomes.

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