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Predictors and Features of Interstitial Lung Disease in Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis is a rare autoimmune disorder. The study aimed to assess the predictors and features of interstitial lung disease in patients with rheumatoid arthritis.

Methods: A retrospective study was conducted in the Pulmonology Department of Ibn-e- Siena Hospital, Multan, from August 2024 to August 2025. 200 patients diagnosed with rheumatoid arthritis who underwent pulmonary high-resolution computed tomography scan were included in the study by non-probability consecutive sampling. Based on the results of lung CT, patients were categorized according to the presence or absence of ILD. Data analysis was done by SPSS version 23. ANOVA, t-test and rank sum test were performed to assess quantitative variables, which were compared by x2 test. Statistical significance was set at a probability value of less than 0.05.

Results: A total of 86 patients (43%) with RA had interstitial lung disease. The most frequent manifestation in patients with ILD was non-specific interstitial pneumonia pattern in 50 patients (58.2%). The biochemical parameters, including globulin (p=0.005), gamma glutamyl transpeptidase (p=0.031), erythrocyte sedimentation rate (p=0.004), lactate dehydrogenase (p<0.001), CRP (p=0.022) and rheumatoid factor positive (p=0.026) were significantly elevated in ILD positive patients. Multivariate analysis showed age (OR: 1.601, 95% CI: 1.21-2.11), smoking (OR: 2.122, 95% CI: 1.35-3.76), rheumatoid factor (OR:1.689, 95% CI: 1.03-2.78), RA onset duration (OR: 0.373) and lactate dehydrogenase levels (OR: 7.374, 95% CI: 3.24-16.75) as independent risk factors of RA-ILD.

Conclusion: The incidence of interstitial lung disease in rheumatoid arthritis patients was 43% with advanced age, smoking, duration of RA onset and positive rheumatoid factor as independent predictor of incidence of ILD. Given the significant association with elevated inflammatory markers and high mortality risk, early HRCT screening is essential for timely diagnosis and improved management.

Keywords: Arthritis, Interstitial Lung Disease, Predictors, Rheumatoid Arthritis

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INTRODUCTION

Rheumatoid arthritis is a rare but severe autoimmune disorder of hands and feet occurring in 0.5-1% patients[1]. It primarily affects the joints but also causes inflammation in the heart, lungs, eyes, skin, kidneys and blood vessels in 50% of patients[2]. In lungs, RA commonly manifests as interstitial lung disease in 3.7-80% patients[3, 4]. Rheumatoid arthritis related to ILD is characterized by inflammation, which can worsen into end-stage fibrosis.

RA-ILD is heterogenous, manifesting in various radiological and pathological patterns, most notably Non-Specific Interstitial Pneumonia (NSIP) and Usual Interstitial Pneumonia (UIP). Distinguishing between these types is critical for prognosis, as the UIP pattern is typically associated with more aggressive fibrosis and poorer survival. While High-Resolution Computed Tomography (HRCT) is the primary diagnostic tool used to identify these patterns, modes of biopsy such as surgical lung biopsy or transbronchial cryobiopsy. Identifying the specific histological subtype is essential for tailoring treatment, as NSIP often shows better responsiveness to immunosuppression than UIP.

Half of the patients with rheumatoid arthritis present with ILD at an early stage or within 3 years of RA diagnosis[5]. The risk of mortality is three times increased in these patients with a mean survival duration of 2.6 years[6]. Hence, these patients have a shorter life span and poor quality of life in addition to high health costs.[7] But still, the risk factors and causes of RA-ILD have not been studied in depth.

The relationship between RA pharmacotherapy and ILD is complex. While traditional disease-modifying antirheumatic drugs (DMARDs) like methotrexate are cornerstones of joint management, they have historically been scrutinized for potential drug-induced pneumonitis. Conversely, newer biological agents and antifibrotics are being investigated for their potential to stabilize lung function. Understanding whether specific medications exacerbate or mitigate pulmonary inflammation is a critical factor in the holistic management of RA-ILD patients.

The rationale of this research was to explore features and predictors of RA-ILD to clarify the biomarkers that can aid with early diagnosis, which is otherwise not possible at an early stage.[8] The features were analyzed by pulmonary imaging, lung function evaluation, physical exam and clinical signs. The identification of these factors can help to improve the therapeutic treatments. While clinical and radiological features are primary diagnostic tools, current research increasingly emphasizes lung histopathology to definitively identify ILD subtypes (such as UIP vs. NSIP) to tailor

precision therapies. Although this study relies on non-invasive pulmonary imaging, the most common approach in clinical practice i.e incorporating histopathological data remains the gold standard for refining diagnosis and guiding advanced treatment strategies. This study aimed to assess the predictors and features of interstitial lung disease in patients with rheumatoid arthritis.

METHODS

A retrospective study was conducted in the Pulmonology Department of Ibn-e- Siena Hospital, Multan, from August 2024 to August 2025. Patients diagnosed with rheumatoid arthritis who underwent a pulmonary high-resolution CT scan were included in the study by non-probability consecutive sampling. By using the WHO calculator, a sample size of 200 cases was calculated with 5% significance level, 80% power of the study and a 95% confidence interval. Patients with a previous diagnosis of pulmonary infarction, emphysema, bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary heart disease, tuberculosis or other respiratory disorders, severe kidney and liver dysfunction, tumors, nodular disease, myocardial infarction and rheumatic heart disease were excluded While conditions such as bronchiectasis and pulmonary heart disease can indeed be sequelae of advanced ILD, they were excluded from the initial study cohort to ensure that the baseline biochemical and radiological markers analyzed were representative of primary RA-ILD rather than confounding secondary complications . By excluding pre-existing tuberculosis and other chronic respiratory disorders, the study aimed to isolate the specific inflammatory and fibrotic patterns directly attributable to the autoimmune progression of RA.

All patients provided written consent to be included in the study. The ethical committee of the hospital approved the study by **Ref No.C-78-1032-A.** Patients' baseline information, such as age, sex, duration since rheumatoid arthritis onset, smoking status, family history of RA, clinical symptoms, lung function, findings of lung CT, echocardiography and biochemical and immunological parameters were recorded. Based on the results of lung CT, patients were categorized according to the presence or absence of ILD by analysis from respiratory, radiology and rheumatology department.

Data analysis was done by SPSS version 23. Normally distributed data were presented by mean ± standard deviation, and non-normally distributed data were presented by median (IQR). ANOVA, t-test and rank sum test were performed to assess quantitative variables, which were compared by x^2 test. Logistic regression analysis identified the risk factors of RA-ILR. Statistical significance was set at a probability value of less than 0.05.

RESULTS

Table I: Baseline Demographic and Clinical Features of Patients According to Incidence of ILD

Variables	RA-ILD positive (n=86)	RA-ILD negative (n=114)
Mean age	58.8 ± 12.8	48.2 ± 15.1
Gender		
Male	35 (40.7%)	45 (39.4%)
Female	51 (59.3%)	69 (60.5%)
Mean disease duration	23 ± 6.2 months	47 ± 8.5 months
Smokers	35 (30.7%)	7 (6.2%)
Clinical manifestations (articular manifestations, respiratory manifestations& extra articular manifestations)	35 (40.7%)	6 (5.3%)
Extra-articular manifestations		
Rheumatoid nodules	6 (7%)	7 (6.2%)
Pericardial effusion	1 (1.2%)	1 (0.9%)
Secondary Sjogren's syndrome	25 (29.1%)	38 (33.4%)
Shortness of breath	26 (74.5%)	2 (33.3%)
Cough	21 (60%)	1 (16.6%)
Fever	9 (25.8%)	3 (50%)
Clubbing	5 (14.5%)	-
Velcro tone	35 (100%)	2 (33.3%)
Pulmonary function (n=60)		
Restrictive ventilatory dysfunction	10/36 (28%)	2/24 (8.7%)
Obstructive ventilatory dysfunction	9/36 (25%)	
Diffuse dysfunction	32/26 (89%)	18/24 (75%)

A total of 200 patients with rheumatoid arthritis were included, with a mean age of 60 ± 14.2 years. 60 patients (30%) were male, and 140 patients (60%) were female. The median age at RA diagnosis was 52 years (IQR: 44-60), with a mean disease duration of 9 years (IQR: 5-13). 86 patients (43%) were RA-ILD positive, among which 12 patients (14%) had ILD before RA onset, 60 patients (69.8%) were diagnosed with ILD after 10 years of RA onset and 14 (16.2%) patients were diagnosed with ILD after more than 10 years. The pulmonary symptoms preceded the articular manifestations, and the patients were only investigated for rheumatoid arthritis following the later onset of joint-related symptoms **Table 1**.

Table 2: Manifestations of Rheumatoid Arthritis in RA-ILD Patients Based on lung HRCT findings (n=86)

Manifestations	N (%)
Non-specific interstitial pneumonia pattern	50 (58.2%)
Pleural thickness	49 (57%)
Reticular patterns	49 (56.9%)
Ground glass attenuation	45 (52.4%)
Thickening of bronchovascular bundles	31 (36.1%)
Interlobular septum thickening	30 (34.9%)
Lung nodules	17 (19.8%)
Emphysematous bullae	17 (19.8%)
Usual interstitial pneumonia	15 (17.5%)
Honeycombing	15 (17.5%)
Bronchiectasis	15 (17.5%)
Subpleural arc line	7 (8.2%)
Subpleural nodules	5 (5.9%)
Pleural effusion	5 (5.9%)
Mediastinal lymph node enlargement	5 (5.9%)

The most frequent manifestation in the RA-ILD positive group was non-specific interstitial pneumonia pattern in 50 patients (58.2%). This was followed by pleural thickening in 49 patients (57%), bronchovascular bundle thickening in 31 patients (36.1%), bronchiectasis in 15 patients (17.5%) and pulmonary hypertension in 8 patients (9.4%), which were significantly higher than the

incidence of 29%, 10.6%, 11.4% and 4.4%, respectively, in the RA-ILD negative group (p=0.000, p=0.000, p=0.009, p=0.006, respectively) **(Table 2).**

Table 3: Comparison of Laboratory Parameters between Groups

Parameters	RA-ILD positive (n=86)	RA-ILD negative (n=114)	t/ Z/ x^2 test	P -value
Globulin	37 ± 6	35 ± 6	-2.89^t	0.005
Lactate dehydrogenase	175 (150-219)	153 (130-179)	-5.030^z	<0.001
Gamma-glutamyl transpeptidase	29 (21-49)	26 (18-41)	-2.198^z	0.031
Erythrocyte sedimentation rate	50 (29-75)	39 (24-66)	-2.983^z	0.004
C-reactive protein	2.5 (1.0-6.7)	1.8 (0.9-4.9)	-2.339^z	0.022
Rheumatoid factor positive	80.5	72.1	4.174^{x2}	0.026
Rheumatoid factor titer	122 (29,508)	85.3 (1341)	-1.876^z	0.053

The biochemical parameters, including globulin (p=0.005), gamma glutamyl transpeptidase (p=0.031), erythrocyte sedimentation rate (p=0.004), lactate dehydrogenase (p<0.001), CRP (p=0.022) and rheumatoid factor positive (p=0.026) were significantly elevated in ILD positive patients **(Table 3).**

Table 4: Univariate analysis

Variable	OR	95% CI	P-Value
Age	1.45	1.12-1.88	0.003
Smoking	2.38	1.28-4.42	0.006
RH positive	1.72	1.03-2.87	0.039
LDH	6.80	2.90-15.91	<0.001

Univariate analysis of variables is shown in **Table 4**.

Table 5: Multivariate Logistic Regression Analysis for Risk factors of RA-ILD

Factors	OR	95% CI	B	P value
Age	1.601	1.21-2.11	0.468	<0.001
Duration of disease				
1-5 years vs 1 year	0.589	0.34-1.04	-0.517	0.071
5-10 years vs 1 year	0.727	0.41-1.30	-0.311	0.289
More than 10 years vs 1 year	0.373	0.20-0.67	-1.000	0.001
Smoking	2.122	1.35-3.76	0.747	0.001
Rheumatoid factor	1.689	1.03-2.78	0.530	0.038
Lactate dehydrogenase	7.374	3.24-16.75	1.966	<0.001
Constant	0.001		-6.931	<0.001

.Multivariate analysis showed age (OR: 1.601, 95% CI: 1.21-2.11), smoking (OR: 2.122, 95% CI: 1.35-3.76), rheumatoid factor (OR:1.689, 95% CI: 1.03-2.78), RA onset duration (OR: 0.373) and lactate dehydrogenase levels (OR: 7.374, 95% CI: 3.24-16.75) as independent risk factors of RA-ILD. **(Table 5).** There was a 60% higher risk of developing ILD with every 10-year increase in age. Patients with RA for 10 years or less were at 65% higher risk of ILD than patients with longer disease duration

DISCUSSION

The results of the study showed that the incidence of ILD was dependent upon duration of RA, and patients with a duration of 10 years or less were at a higher risk. Patients with RA for 10 years or less were at 65% higher risk of ILD than patients with longer disease duration. There was a significantly high number of swelling joints in the RA-ILD positive group,indicating that ILD was associated with disease activity. Hence, the disease activity was higher during 1-10 years of disease onset, and ILD is prevalent in early RA stages. This is backed by previous literature that reports the lung lesions seen on high-resolution CT scan are linked to RA activity, leading to faster disease progression and poor outcomes[9, 10].

Age, smoking, rheumatoid factor positivity and high level of lactate dehydrogenase were independent predictors of RA-ILD. Other studies have also reported smoking, male gender, age, high rheumatoid factor titer and HLA-DR4 positive as predictors of RLA-ILD[11, 12, 13]. In contrast to the present study, anti-CCP has also been linked with joint damage and respiratory manifestations in RA patients[14,15].

Smokers were at higher risk of developing ILD as compared to non-smokers, which is consistent with a previous study, however, we did not study the impact of frequency of smoking on ILD incidence[16]. The risk of ILD also increased with age, with a 60% higher likelihood with each 10-year increase in the current study, similar to previous data[17].A systematic review found that RA patients older than 65 years were at four times higher risk of ILD, suggesting regular screening in the elderly population[18].

The histopathological features of ILD, including usual interstitial pneumonia and non-specific interstitial pneumonia, are common in RA patients, among which the former is related to smoking. In the present study, the NSIP pattern was the most common feature, found in 58.2% patients by HRCT radiological criteria, which is higher than previously reported [19,20]. A study showed that ground glass attenuation was the most common manifestation[21]. The majority of our population was female, all of whom were non-smokers, and ILD manifested as honeycombing in later stages, so it is suggested that all RA patient, male and female, undergo HRCT at the time of onset. 44% of the patients had pulmonary disorders as seen on HRCT, which is similar to some studies,[22,23] but a higher incidence was reported inothers[24, 25]

Our study has some limitations. We only conducted the study in a single hospital with a limited sample size. Secondly, we did not study peripheral blood biomarkers such as anti-CCP and KL-6 of rheumatoid arthritis, which may have contributed to the incidence of ILD.

CONCLUSION

The incidence of interstitial lung disease in rheumatoid arthritis patients was 43% with advanced age, smoking, duration of RA onset and positive rheumatoid factor as independent predictor of incidence of ILD. Given the significant association with elevated inflammatory markers and high mortality risk, early HRCT screening is essential for timely diagnosis and improved management.

FUNDING

None.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

The study was conducted after approval from the ethical committee of the hospital, under **Ref No.C-78-1032-A**.

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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