



Original Article



Clinical, Serological and Radiological Profile of Patients with Autoimmune Disease Associated Interstitial Lung Disease

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ABSTRACT

The clinical, serological, and radiological profiles of interstitial lung disease in patients with autoimmune diseases vary significantly and are poorly studied. **Objectives:** To determine the clinical, serological and radiological profile of patients with autoimmune-associated interstitial lung disease. **Methods:** This cross-sectional study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period from 16th December 2023 to 15th December 2024. A total of 105 male and female patients in the age range of 40 to 80 years diagnosed with autoimmune-related interstitial lung disease were studied. History, clinical examination, blood tests and high-resolution computerized tomographic (HRCT) scan were performed to determine the clinical, serologic and radiologic features of AI-ILD. **Results:** The mean age of the participants was 51.51 ± 12.34 years. Female patients outnumbered men ($n=61, 58.1\%$). Arthritis was most commonly recorded in 47 participants (44.8%) followed by skin rash ($n=33, 31.4\%$). Antinuclear antibody (ANA) and anti-dsDNA (double-stranded deoxyribonucleic acid) constituted the most frequently found serological factors observed in 32 (30.5%) and 28 (26.7%) patients, respectively. Usual interstitial pneumonia was observed in 19 patients (17.4%), non-specific interstitial pneumonia in 36 (34.2%) and lymphoid interstitial pneumonia was recorded in 7 participants (6.7%). **Conclusions:** It was concluded that middle-aged women with inflammatory arthritis and skin rashes with rheumatoid arthritis as background disease were more likely to have interstitial lung disease. Serologic factors lack specificity. The most common radiological finding on HRCT was ground glass opacities and non-specific interstitial pneumonia as the most frequent radiological diagnosis.

INTRODUCTION

Connective tissue disorder encompasses a group of pathological conditions characterized by inflammatory damage to extracellular matrix and collagen and elastin proteins [1]. The process is immune-mediated in most instances. Persistent insult to supporting connective tissue results in permanent damage and loss of organ function. The disorder has two components: genetic predisposition and an environmental autoimmune factor [2]. Common types of connective tissue disease include rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, Sjögren syndrome and systemic sclerosis. The pulmonary element of such autoimmune connective tissue disease is referred to as interstitial lung disease [3]. Interstitial lung disease (ILD)

refers to a heterogeneous group of clinical conditions that affect the lung parenchyma, arising from a variety of causes. Often, the underlying etiological factor is unidentified, commonly referred to as idiopathic interstitial pneumonia (IIP) [4]. It represents a unique category that leads to damage in the lung parenchyma with different patterns of inflammation and fibrosis. IIP is divided into several categories based on histological and radiological characteristics. Each pattern necessitates a thorough investigation into its potential causes [5]. The clinical spectrum of pulmonary involvement in autoimmune disease is very wide, ranging from completely asymptomatic to sequela related to advanced fibrosis. Early diagnosis and treatment of pulmonary involvement in



autoimmune disease is critical since it is a major cause of mortality and morbidity in such patients [6]. Several pulmonary structures could be affected simultaneously including the lung parenchyma, pleura, bronchi and the airways. Permanent damage results in fibrous replacement of pulmonary tissue, commonly known as idiopathic pulmonary fibrosis. High resolution CT scan is often required to diagnose the pulmonary component of autoimmune disease, pulmonary fibrosis and the extent of fibrosis [7]. Initially, diagnosis is often suggested by pulmonary function tests. In a meta-analysis, the prevalence of ILD in patients with rheumatoid arthritis was 11%, 47% in systemic sclerosis, 41% in inflammatory myositis, 17% in Sjögren Syndrome, 56% in mixed connective tissue disorder and 6% in SLE [8]. There is a lack of comprehensive data focusing on the specific characteristics of autoimmune-related interstitial lung disease (AI-ILD) across different autoimmune diseases. The clinical, serological, and radiological profiles of interstitial lung disease patients provide critical insights into disease onset, progression, and prognosis. The clinical manifestations of AI-ILD vary significantly, moreover serological pattern is poorly studied. There is a need for more standardized radiological criteria that can aid in distinguishing AI-ILD from other forms of ILD. There is a scarcity of studies that focus specifically on AI-ILD as a distinct entity.

This study aims to investigate the collective features of AI-ILD, helping clinicians identify common patterns and prognostic indicators across different autoimmune diseases. Ultimately, the findings would contribute to a better understanding of AI-ILD, facilitating early diagnosis, targeted therapies, and improved patient outcomes.

METHODS

This cross-sectional study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period from 16th December 2023 to 15th December 2024. Approval for the conduct of the study was obtained vide no 32/DME/KMC. Male and female patients in the age range of 40 to 80 years diagnosed with autoimmune-related interstitial lung disease were studied. Patients with active or previous history of pulmonary tuberculosis, bronchogenic carcinoma, secondaries in the lung, history of drug-related pulmonary fibrosis and severe cardiopulmonary compromised patients were excluded. The sample size was 105, which was calculated taking 11.0% anticipated prevalence of ILD in autoimmune disease (rheumatoid arthritis), 6% margin of error and 95% confidence level [8]. Participants were enrolled using a non-probability consecutive sampling technique. Interstitial lung disease was confirmed on a high-resolution CT scan of the lung, showing reticular pattern with ground glass opacities and architectural distortion of

interstitial tissue. Autoimmune disease included 1) Rheumatoid Arthritis: Presence any four among morning stiffness, arthritis, soft tissue swelling, subcutaneous nodules, positive serology and radiological features of bone erosion 2) Systemic Lupus Erythematosus: Positive ANA and atleast 10 score among fever, leucopenia, thrombocytopenia, hemolysis, seizure, psychosis, delirium, malar rash, discoid rash, oral ulcer, effusion, pericarditis, arthritis, renal involvement, positive antiphospholipid, low C3 and positive SLE specific antibodies. 3) Systemic Sclerosis: Score 9 among fingertip lesions, skin tightening, telangiectasias, pulmonary hypertension, Raynaud's phenomenon, arthritis, esophagitis, sclerodactyly, abnormal nailfold capillaries and positive antibodies. 4) Inflammatory Myositis: Progressive symmetrical muscle weakness, raised muscle enzymes, dysphagia, respiratory muscle weakness, skin rash and muscle biopsy consistent with inflammation. 5) Sjögren Syndrome: Dry mouth, dry eyes, oral ulcers, positive antibodies and positive Schirmer test. Clinical features included: Pulmonary features including chest pain, shortness of breath, cough and sputum and extra-pulmonary features included GI, joint, skin and renal features. Serological Features studied included: Rheumatoid factor, anti-CCP, ANA, anti-SSA, anti-SSB, anti-Scl 70, anti-ds-DNA, anti-Smith, anti-Scl 70 and anti-RNA proteins. Radiological features included: ground glass appearance, reticular pattern, cysts, honeycomb, pulmonary hypertension, non-specific interstitial pneumonia, usual interstitial pneumonia and lymphoid interstitial pneumonia. Informed consent was obtained from enrolled participants. Baseline features such as age, gender, BMI, smoking history, comorbidities like diabetes, hypertension, ischemic heart disease and medications were noted. History was taken about pulmonary and extra-pulmonary complaints. Pulmonary symptoms noted included: Dyspnea: Modified BORG dyspnea scale >4, Cough: visual analogue scale >4 and chest pain (VAS>4). Clinical examination was carried out, starting with a general physical examination. Pulse. Blood pressure and respiratory rate were noted. A detailed examination of the front and back of the chest was carried. All systems were reviewed, including GI, joint, skin and renal and findings were noted. Tests analyzing pulmonary functions were carried out, and blood samples were taken, and a thorough autoimmune profile was performed for serological features. HRCT films were reviewed by two independent consultant radiologists for the presence of pneumonia and its types. Findings were noted in the case of agreement. In case of disagreement, a third opinion from the senior-most radiologist was taken, which was considered final. Data were analyzed using SPSS version 26.0. Means and standard deviations were recorded for continuous data like age, BMI and duration of complaints, while frequencies and

percentages were recorded for qualitative data like gender, smoking history, clinical features, serological and radiological features. Effect modifiers were controlled through stratification. Post-stratification chi-square test of association was applied. p -values ≤ 0.05 was considered significant.

RESULTS

The mean age of the participants was 51.51 ± 12.34 years. The Majority of the patients were aged more than 50 years ($n=59$, 56.2%). Male participants were 44 (41.9%), and 73 patients (69.5%) had a BMI less than 25.0kg/m². Illness duration less than 30 months was observed in 32 patients (30.5%). 60 patients (57.1%) belonged to the rural population (Table 1).

Table 1: Socio-Demographic and Baseline Clinical Parameters of Study Cohort ($n=105$)

Parameters	Subgroups	n (%)
Age (Years) (Mean 51.51 ± 12.349)	50 or Below	46 (43.8%)
	More Than 50	59 (56.2%)
Gender	Male	44 (41.9%)
	Female	61 (58.1%)
BMI (kg/m ²) (Mean 23.994 ± 2.6961)	25.0 or Below	73 (69.5%)
	More Than 25.0	32 (30.5%)
Illness Duration (Months) (Mean 34.02 ± 4.977)	30 or Below	32 (30.5%)
	More Than 30	73 (69.5%)
Education	Above Matric	42 (40.0%)
	Matric or Below	63 (60.0%)
Profession	Employed	26 (24.8%)
	Unemployed	79 (75.2%)
Residence	Rural	60 (57.1%)
	Urban	45 (42.9%)
SE Status	Fair	30 (28.6%)
	Poor	75 (71.4%)
Smoking History	Yes	19 (18.0%)
	No	86 (82.0%)
Hypertension	Yes	35 (33.3%)
	No	70 (66.7%)
Diabetes	Yes	23 (21.9%)
	No	82 (78.1%)

Rheumatoid arthritis was the most common background diagnosis out of all 105 patients recorded in 44 (41.9%), followed by SLE ($n=25$, 23.8%). Myositis and Sjögren were least prevalent, recorded in 10 patients (9.5%) each (Figure 1).

Background Autoimmune Disease

■ RA ■ SLE ■ Systemic Scl ■ Sjogren Syndrome ■ Myositis

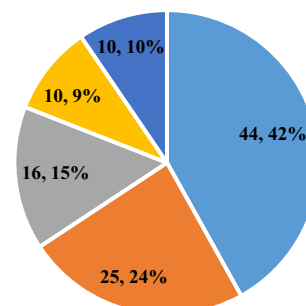


Figure 1: Background Autoimmune Disease of Study Cohort ($n=105$)

In terms of clinical signs and symptoms of background disease, arthritis was most commonly recorded in 47 participants (44.8%), followed by GI complaints ($n=37$, 35.2%), skin rash ($n=33$, 31.4%) and Raynaud's phenomena ($n=16$, 15.2%), respectively (Table 2).

Table 2: Clinical Signs and Symptoms of Study Cohort ($n=105$)

Clinical Parameters		Frequency (%)
Skin rash	Yes	33 (31.4%)
	No	72 (68.6%)
Arthritis	Yes	47 (44.8%)
	No	58 (55.2%)
Raynaud's Phenomenon	Yes	16 (15.2%)
	No	89 (84.8%)
GI Symptoms	Yes	37 (35.2%)
	No	68 (64.8%)

ANA (antinuclear antibodies) and anti-dsDNA (anti-double-stranded DNA) constituted the most frequently found serological factors observed in 32 (30.5%) and 28 (26.7%) patients, respectively. Anti-CCP was observed in 19 patients (18.1%), RA factor in 18 (17.1%), anti-SSA and anti-SSB in 19 (18.1%) and 23 (21.9%) patients, respectively (Table 3).

Table 3: Serological Parameters of Study Cohort ($n=105$)

Serological Profile		Frequency (%)
ANA	Yes	32 (30.5%)
	No	73 (69.5%)
Anti CCP	Yes	19 (18.1%)
	No	86 (81.9%)
Anti Scl 70	Yes	17 (16.2%)
	No	88 (83.8%)
Anti Ro 52	Yes	17 (16.2%)
	No	88 (83.8%)
RA factor	Yes	18 (17.1%)
	No	87 (82.9%)
Anti SSA	Yes	19 (18.1%)
	No	86 (81.9%)
Anti SSB	Yes	23 (21.9%)
	No	82 (78.1%)

Anti-ds DNA	Yes	28 (26.7%)
	No	77 (73.3%)
Anti-Smith	Yes	21 (20.0%)
	No	84 (80.0%)

Ground glass opacities were the most frequent radiological findings on HRCT (n=71, 67.6%), followed by reticular pattern (n=65, 61.9%) and fibrosis in 58 patients (55.2%). Usual interstitial pneumonia was observed in 19 patients (17.4%), non-specific interstitial pneumonia in 36 (34.2%) and lymphoid interstitial pneumonia was recorded in 7 participants (6.7%) (Table 4).

Table 4: Confidence Intervals for Key Outcomes

Radiological Findings		Frequency (%)
Ground Glass Opacities	Yes	71 (67.6%)
	No	34 (32.4%)
Reticular Pattern	Yes	65 (61.9%)
	No	40 (38.1%)

Fibrosis	Yes	58 (55.2%)
	No	47 (44.8%)
Honey Combing	Yes	42 (40.0%)
	No	63 (60.0%)
Cysts	Yes	49 (46.7%)
	No	56 (53.3%)
Radiological Diagnosis	Pulmonary Artery Hypertension	43 (40.9%)
	Usual Interstitial Pneumonia	19 (17.4%)
	Non - Specific Interstitial Pneumonia	36 (34.2%)
	Lymphoid Interstitial Pneumonia	07 (6.7%)

Skin rash was the predominant complaint in 54.5% of patients with SLE. The p-value for the association between skin rash and autoimmune disease was significant (<0.05). Similarly, arthritis was prevalent in RA patients (100.0%). The chi-square p-value was 0.018, which was significant (Table 5).

Table 5: Stratification of Clinical Parameters with Autoimmune Disease Subtypes (n=105)

Clinical Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Scleriosis	Sjogren's	Myositis		
Skin Rash	Yes	05 (15.5%)	18 (54.5%)	8 (24.2%)	0 (0.0%)	2 (6.1%)	33 (100%)	0.011
	No	39 (54.1%)	07 (9.7%)	8 (11.1%)	10 (13.9%)	8 (11.1%)	72 (10%)	
Arthritis	Yes	44 (93.6%)	02 (4.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	47 (100%)	0.018
	No	0 (0.0%)	23 (39.6%)	15 (25.8%)	10 (17.2%)	10 (17.2%)	58 (100%)	
Raynaud	Yes	6 (37.5%)	4 (25.0%)	4 (25.0%)	2 (12.5%)	0 (0.0%)	16 (100%)	0.517
	No	38 (42.7%)	21 (23.6%)	12 (13.5%)	8 (9.0%)	10 (11.2%)	89 (100%)	
GI Symptoms	Yes	17 (45.9%)	6 (16.2%)	4 (10.8%)	4 (10.8%)	6 (16.2%)	37 (100%)	0.274
	No	27 (39.7%)	19 (27.9%)	12 (17.6%)	6 (8.8%)	4 (5.9%)	68 (100%)	

Anti-CCP was positive in 26.3% of patients with rheumatoid arthritis (RA) and 31.6% of patients with systemic sclerosis. The p-value for the association between anti-CCP and autoimmune diseases was significant (<0.05) (Table 6).

Table 6: Stratification of Serological Parameters with Autoimmune Disease Subtypes (n=105)

Serological Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Scleriosis	Sjogren's	Myositis		
ANA	Yes	14 (43.8%)	10 (31.3%)	2 (6.3%)	4 (12.5%)	2 (6.3%)	32 (100.0%)	0.343
	No	30 (41.1%)	15 (20.5%)	14 (19.2%)	6 (8.2%)	8 (11.0%)	73 (100.0%)	
Anti CCP	Yes	5 (26.3%)	2 (10.5%)	6 (31.6%)	0 (0.0%)	6 (31.6%)	19 (100.0%)	0.000
	No	39 (45.3%)	23 (26.7%)	10 (11.6%)	10 (11.6%)	4 (4.7%)	86 (100.0%)	
Anti Ro52	Yes	9 (52.9%)	6 (35.3%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	17 (100.0%)	0.144
	No	35 (39.8%)	19 (21.6%)	16 (18.2%)	8 (9.1%)	10 (11.4%)	88 (100.0%)	
Anti-Scl 70	Yes	9 (52.9%)	2 (11.8%)	4 (23.5%)	2 (11.8%)	0 (0.0%)	17 (100.0%)	0.311
	No	35 (39.8%)	23 (26.1%)	12 (13.6%)	8 (9.1%)	10 (11.4%)	88 (100.0%)	
RF	Yes	8 (44.4%)	4 (22.2%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	18 (100.0%)	0.981
	No	36 (41.4%)	21 (24.1%)	14 (16.1%)	8 (9.2%)	8 (9.2%)	87 (100.0%)	
Antids-DNA	Yes	12 (42.9%)	6 (21.4%)	6 (21.4%)	2 (7.1%)	2 (7.1%)	28 (100.0%)	0.824
	No	32 (41.6%)	19 (24.7%)	10 (13.0%)	8 (10.4%)	8 (10.4%)	77 (100.0%)	

Ground glass opacities were recorded in 50.7% patients with RA related ILD, reticular pattern was prevalent in 33.8% with RA and 26.2% with SLE. A statistically significant association was recorded between radiological features and various types of autoimmune disease (Table 7).

Table 7: Stratification of Radiological Parameters with Autoimmune Disease Subtypes(n=105)

Serological Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Scleriosis	Sjogren's	Myositis		
Ground Glass Opacities	Yes	36 (50.7%)	13 (18.3%)	14 (19.7%)	6 (8.5%)	2 (2.8%)	71 (100%)	0.000
	No	8 (23.5%)	12 (35.3%)	2 (5.9%)	4 (11.8%)	8 (23.5%)	34 (100%)	
Reticular Pattern	Yes	22 (33.8%)	17 (26.2%)	14 (21.5%)	8 (12.3%)	4 (6.2%)	65 (100%)	0.028
	No	22 (55.0%)	8 (20.0%)	2 (5.0%)	2 (5.0%)	6 (15.0%)	40 (100%)	
Fibrosis	Yes	20 (34.5%)	12 (20.7%)	12 (20.7%)	4 (6.9%)	10 (17.2%)	58 (100%)	0.008
	No	24 (51.1%)	13 (27.7%)	4 (8.5%)	6 (12.8%)	0 (0.0%)	47 (100%)	
Honey Combing	Yes	26 (61.9%)	6 (14.3%)	4 (9.5%)	2 (4.8%)	4 (9.5%)	42 (100%)	0.014
	No	18 (28.6%)	19 (30.2%)	12 (19.0%)	8 (12.7%)	6 (9.5%)	63 (100%)	
Cysts	Yes	16 (32.7%)	9 (18.4%)	10 (20.4%)	6 (12.2%)	8 (16.3%)	49 (100%)	0.044
	No	28 (50.0%)	16 (28.6%)	6 (10.7%)	4 (7.1%)	2 (3.6%)	56 (100%)	

DISCUSSION

In this study, the mean age of participants was 51.51 ± 12.349 years, and the majority of study participants were aging more than 50 years. In a study by Hazarika et al., the mean age was 50.6 years, with 54% of participants aged more than 50 years [8]. This is similar to current observation. In another study, the mean age of the patients with autoimmune-related interstitial lung disease was 54.6 years, which is in coherence with our observation [9]. However, Lim et al., reported a much higher mean age of 67.9 years [10]. The mean age of the participants in a study by Karampeli et al., was 63.2 years, i.e., higher than our observation [11]. The higher prevalence of autoimmune-related interstitial lung disease may be attributed decline in the immune system, prolonged exposure to infectious or other environmental elements, triggering the autoimmune reactions [12]. The majority of our study participants were female. Oldham et al., reported 62.0% female patients as their study population [13]. Lim and colleagues reported 64% of participants [10]. Hazarika et al., and Avala et al., reported 86.6% and 83% female participants, respectively, which were much higher compared to the present study [8, 14]. Male participants outnumbered female participants in another study [5]. Female predominance in autoimmune-related ILD may be attributed to genetic predisposition, endogenous hormonal influence modulating the immunity [15]. Exogenous hormones such as contraceptive pills could also lead to immune overactivity [16]. Arthritis was the most common complaint in our study, followed by GI, skin and Raynaud's phenomenon. Sebastiani et al., reported inflammatory arthritis as the predominant clinical feature among patients with autoimmune-related ILD [17]. Results of a study by Karampeli et al., showed inflammatory arthritis in 82.0% of patients, followed by skin rash (54%) and Raynaud's phenomenon in 25.6% of participants [11]. Though the individual proportions for each characteristic might be variable, the overall pattern of clinical features reflects our results. Similarly, Lim et al., and Avala et al., reported inflammatory arthritis as the most commonly reported complaint in 76.5% and 66.7% of participants,

respectively [10, 14]. Raynaud's phenomenon was the predominant complaint in 27.8% of patients in a study by Oldham and colleagues, followed by inflammatory arthritis (17.4%) [13]. Similar observations were reported by another study [9]. Hazarika et al., reported an equal proportion of inflammatory arthritis and Raynaud's phenomenon in their study [8]. Lungs and joints are most frequently affected in rheumatologic disease because the resemblance in connective tissue of lungs and joints is quite similar, making both organs more susceptible to damage in autoimmune diseases. Difference in proportions of arthritis in different populations may be due to genetic variability, differences in exposure to environmental toxins and the presence of any comorbidities [18, 19]. Antinuclear antibodies (ANA) and anti-ds DNA (anti-double-stranded DNA) were the most frequent serological factors, followed by anti-CCP, RA factor and anti-SSA and B, respectively. ANA was positive in 97.4% of patients (taking 1:100 dilution) and 31.4% (taking 1:320 dilution) of patients, followed by anti-ds DNA in a study by Hazarika et al., [8]. The current study utilized 1:320 as the cut-off for ANA positivity, hence, our findings were close to later reports in a study by Hazarika et al. Other studies have reported similar findings [17, 20]. Speckled pattern ANA was strongly positive in autoimmune-related ILD in a Greek population [11]. Rheumatoid factor was least positive in our study. Our observation was in agreement with the results of studies where only one patient was found with a positive RA factor among the study participants [9, 21]. RA factor was most frequently serologically found positive in patients with autoimmune-related ILD in another study, in contrast to our observation [8]. The proportion of anti-CCP positivity in our study supports the observation of Fischer and colleagues, detected in 17.8% of patients [22]. Ito et al., reported anti-CCP positivity in 13.0% of patients [20]. Hazarika and colleagues reported a similar detection rate (14.3%) [8]. Anti-Scl 70 was found in 16.2% of patients in our study. Anti-Scl 70 is a scleroderma-associated serologic factor and may be found in patients with autoimmune-related ILD. It has been reported that suppression of anti-

Scl 70 with immunosuppression could result in reversal of fibrosis resulting from autoimmune pathogenicity [23]. Ground glass opacities were the most frequent radiological findings on HRCT patients. The most common radiological diagnosis was pulmonary artery hypertension, followed by unusual and usual interstitial pneumonia. The relatively low prevalence of usual interstitial pneumonia concerning ground glass opacities may be because of reporting bias in the current study. Usual interstitial pneumonia was recorded in 54.6% on HRCT, non-specific pneumonia in 31.9% in a study [13]. Another study reported that non-specific pneumonia was the most common HRCT diagnosis in 42.1%, followed by usual pneumonia in 15.8%, which is in agreement with our observation [5]. Ito *et al.*, reported 64.0% cases of non-specific pneumonia as compared to 20.0% cases with usual pneumonia, which is in coherence with our findings [20]. Other studies have shown similar results [12, 23]. Sharma and colleagues reported usual pneumonia as the predominant HRCT diagnosis in contrast to our observation in 35.7% of patients [24]. The difference in results may be explained by several reasons, such as differences in image qualities, artefacts, presence of extra-pulmonary features or reporter interpretation of various findings [25].

CONCLUSIONS

It was concluded that clinical, serologic and radiologic patterns in AI-ILD patients were very wide. Clinically, middle-aged women with inflammatory arthritis and skin rashes with rheumatoid arthritis as background disease were more likely to have interstitial lung disease. ANA and anti-Scl 70, though commonly positive, lack specificity and might be performed as part of a workup, but not diagnostic test. The most common radiological finding on HRCT was ground glass opacities and non-specific interstitial pneumonia as the most frequent radiological diagnosis.

Authors Contribution

Conceptualization: HA

Methodology: HA, MI, IUD, SZ

Formal analysis: IUD, SZ

Writing review and editing: HA, A

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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