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Original Article

Spectrum of Interstitial Lung Disease Patterns in Connective Tissue Diseases and their Outcomes: a Retrospective Analysis

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ABSTRACT

Objective: To evaluate patterns of connective tissue disease-associated interstitial lung disease and to evaluate disease outcomes across various CTD subtypes in a tertiary care setting in Lahore, Pakistan.

Study Design: Observational Retrospective Study

Place and Duration of the Study: Rheumatology Department, Central Park Teaching Hospital, and its affiliated Clinics, Lahore, Pakistan, from 2021 to 2025.

Methodology: The data of 174 patients diagnosed with CTD-ILD was reviewed. Inclusion criteria included adult patients with a confirmed CTD diagnosis (as per ACR/EULAR criteria) and HRCT-confirmed ILD. Data on demographics, serology, HRCT patterns, and pulmonary function tests (PFTs), and outcomes were analyzed using SPSS v27. The statistical significance was set at $p \leq 0.05$.

Results: Among 174 patients, 93.7% were female, with a mean age of 49.4 ± 13.7 years. The most common CTD was systemic sclerosis (30.5%), followed by rheumatoid arthritis (21.8%) and mixed connective tissue disease (MCTD) (19.5%). NSIP was the predominant HRCT pattern (61.5%), followed by UIP (23.0%). Disease activity varied, with active disease most common in SLE (62.5%) and systemic sclerosis (47.2%). PFTs showed moderate to severe restriction in a majority of patients, particularly those with myositis, systemic sclerosis, and SLE ($p < 0.001$).

Conclusion: CTD-ILD presents with heterogeneous clinical, serological, and radiological profiles. NSIP is the most frequent ILD pattern across CTDs. Timely identification of ILD patterns and targeted immunosuppressive therapy may improve patient outcomes.

Keywords: Interstitial lung disease, Mixed connective tissue disease, Pakistan, Retrospective study

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INTRODUCTION

Connective tissue disease (CTD) is a group of autoimmune disorders differentiated by abnormal immune activation and inflammation directed against the body's connective tissues [1]. Interstitial lung disease (ILD) is the most common and clinically significant pulmonary complication associated with CTDs [2]. It can develop in several CTDs, including Rheumatoid arthritis, Systemic lupus erythematosus, Sjögren's syndrome, idiopathic inflammatory myopathies such as dermatomyositis and polymyositis, systemic sclerosis, and mixed connective tissue disease [3].

ILD develops in 40-50% of patients with CTDs, making it a major contributor to disease burden and fatal outcomes in this group [1]. The prevalence of CTD-associated ILD varies depending on disease subtype, classification criteria and study populations, with the highest frequencies reported in SSc and IIM patients, and lower rates observed in SLE [4]. RA and SS exhibit intermediate rates of ILD, yet they represent a significant portion of CTD-ILD cases due to their overall higher occurrence in the general population [5]. Estimated ILD prevalence among CTD subtypes is up to 58% in RA, 13% in SLE, 27% in SS, 80% in DM/PM, 91% in SSc, and 67% in MCTD [6].

In Pakistan, ILDs account for approximately 4.75% of all deaths, while pneumonia and influenza contribute to 14.56% of mortality [7]. CTD-ILD typically follows a chronic and progressive direction. Non-specific interstitial pneumonia (NSIP) is the predominant histopathological pattern, except in RA, where usual interstitial pneumonia (UIP) is more frequently identified. Despite its clinical importance, the pharmacological treatment of CTD-ILD remains poorly defined, with no universally accepted guidelines. Diagnostic evaluations often relies on high-resolution CT (HRCT), bronco-alveolar lavage, and, in selected cases, surgical lung biopsy [8]. The spectrum of interstitial lung diseases may vary between regions due to differences in living standards, environmental

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conditions, occupational risks, lifestyle behaviors, smoking, social practices, agricultural techniques, and underlying genetic factors [7].

Despite the high burden and varied presentation of CTD-ILD, evidence from Pakistan and other South Asian populations remains scarce. Very few studies describe the distribution of ILD patterns across CTDs or their associated clinical outcomes in this region. Most available data originate from Western cohorts, which may not fully reflect the disease patterns in populations exposed to different environmental and genetic factors. This gap underscores the need for region-specific data to inform early diagnosis and management of CTD-ILD. Thus, this is hypothesized that the spectrum and frequency of ILD patterns in Pakistani patients with CTDs differ from those reported internationally, and that certain ILD patterns are associated with distinct clinical outcomes. To address this research gap, this retrospective analysis aims to assess the spectrum of ILD patterns in patients with CTDs and evaluate their clinical outcomes in a tertiary care setting.

METHODOLOGY

This retrospective study was carried out at the Institute of Rheumatic Diseases, Central Park Teaching Hospital, Lahore, and its affiliated clinics in Lahore, Pakistan from 2021 to 2025. Sample size was calculated using the World Health Organization (WHO) sample size calculator taking confidence level 95%, 5% margin of error, and a prevalence of ILD in mixed connective tissue disease of 9.7%[9] based on previously published data. The minimum required sample size was 135 patients; however, a total of 172 patients were included in the study to enhance the precision and power of the analysis. A non-probability consecutive sampling technique was applied, and all eligible cases meeting the diagnostic criteria during the study period were included.

Inclusion Criteria: Patients aged 18 years or older of either gender who had a confirmed diagnosis of any CTD according to ACR/EULAR classification criteria and radiologically confirmed interstitial lung disease (ILD) on high-resolution computed tomography (HRCT). Patients were also required to have at least one follow-up visit documenting disease activity or clinical outcome.

Exclusion Criteria: Patients with ILD of non-autoimmune etiology (idiopathic pulmonary fibrosis, occupational lung disease), those with incomplete clinical or radiological records, missing HRCT data, or those lost to follow-up within three months of ILD diagnosis.

Ethical approval for this study was granted by the Institutional Review Board of Central Park Medical College and Teaching Hospital, Lahore (No: CPMC /IRB-No/1511A; Date: 15th January 2025). Patient confidentiality was maintained by anonymizing all data prior to analysis. Information such as names, contact details, and hospital numbers were removed, and each case was assigned a unique study code. As this was a retrospective study, the requirement for written informed consent was waived and an exemption was approved by IRB.

Data were extracted from the hospital's electronic medical record system for all CTD-ILD patients. Extracted information included demographic details, clinical characteristics, serological markers, HRCT findings, and outcome data. Completeness and accuracy of records were verified independently by two rheumatologists, who cross-checked clinical files with HRCT images, serology results, and follow-up entries. HRCT scans were reviewed by experienced radiologists, and ILD patterns were classified as non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), fibrotic NSIP, or indeterminate. Disease activity was assessed based on the treating physician's global assessment documented in clinical notes. Pulmonary function was categorized using standard PFT interpretation criteria into normal, mild, moderate, or severe restriction.

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 27 software. Normality of continuous variables was assessed using the Shapiro-Wilk test. Age, treatment duration, primary disease onset, and ILD onset were all non-normally distributed ($p < 0.05$ for all variables). Therefore, these variables were summarized using median and interquartile range (IQR). On the other hand, qualitative variables were presented as frequencies and percentages. The chi-square test or Fisher's exact test was applied to evaluate associations between categorical variables, with a focus on outcomes across various CTD subtypes and ILD patterns. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Of the 174 patients, 11(6.3%) were male and 163 (93.7%) were female, with F/M ratio of approximately 14.8:1. The median age at the time of presentation was

50 years, with the largest proportion of patients falling in the 46-60 year age group (36.8%), followed by 31-45 years (31%). The median duration of underlying connective tissue disease (CTD) was 8 years, while the median duration since the diagnosis of ILD was 6 years. The general demographic and clinical characteristics of the patients are exhibited in Table I.

Table I: Demographic and Clinical Profile of Respondents (n=174)

Parameters	Categories		values
Age (years)	Median (IQR)		50 (21)
Age group (years)	18-30		16 (9.2%)
	31-45		54 (31%)
	46-60		64 (36.8%)
	61-75		36 (20.7%)
	76-90		4 (2.3%)
Gender	Male		11 (6.3%)
	Female		163 (93.7%)
Duration since the onset of CTD (years)	Median (IQR)		8 (8.5)
Duration since the onset of ILD (years)	Median (IQR)		6 (5)
Treatment period (years)	Median (IQR)		6 (8)
CTDs	SSc		53 (30.5%)
	RA		38 (21.8%)
	MCTD		34 (19.5%)
	Myositis		5 (2.9%)
	SLE		8 (4.6%)
	Sjögren's syndrome		15 (8.6%)
	IPAF		21 (12.1%)
ILD patterns on HRCT	NSIP		107 (61.5%)
	UIP		40 (23%)
	LIP		22 (12.6%)
	Fibrosing NSIP		1 (0.6%)
	Indeterminate		4 (2.3%)
Treatment	DMARDS	MMF	131 (75.3%)
		Azathioprine	19 (10.9%)
		Tacrolimus	0 (0)
		Leflunamide	20 (11.5%)
	Biologics	Rituximab	22 (12.6%)
		Tocilizumab	6 (3.4%)
		None	145 (83.3%)
	Addition of Nintedanib	Yes	4 (2.3%)
		No	168 (96.6%)
	Addition of prednisolone	Yes	145 (83.3%)
		No	25 (14.4%)
	Dose of prednisolone	1mg	3 (1.7%)
		2mg	8 (4.6%)
		2.5mg	8 (4.6%)
		5mg	73 (42%)
		7mg	15 (8.6%)
		10mg	45 (25.9%)
		30mg	1 (0.6%)
Serological findings	ANA	Yes	128 (73.6%)
		No	30 (17.2%)
	PM-SCL	Yes	4 (2.3%)
		No	152 (87.4%)
	Anti Ro Anti La	Yes	41 (23.6%)
		No	113 (64.9%)
	PL-12	Yes	4 (2.3%)
		No	147 (84.5%)
	Anti Scl 70	Yes	35 (20.1%)
		No	118 (67.8%)
	Anti Sm	Yes	2 (1.1%)
		No	148 (85.1%)
	Anti ds DNA	Yes	12 (6.9%)
		No	141 (81%)
	Anti Ku	Yes	5 (2.9%)
		No	148 (85.1%)
	Anti RNP	Yes	27 (15.5%)
		No	124 (71.3%)
	Anti Mi2	Yes	2 (1.1%)
		No	149 (85.6%)

**SD: Standard deviation; CTD: Connective tissue disease; ILD: Interstitial lung disease; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; MCTD: Mixed connective tissue disease, SLE: Systemic lupus erythematosus; IPAF: Interstitial pneumonia with autoimmune features; NSIP: Non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia; LIP: Lymphocytic interstitial pneumonia; PFT: Pulmonary function test; DMARD: Disease-modifying anti-rheumatic drug; MMF: Mycophenolate mofetil; ANA: Antinuclear antibody; PM-Scl: Anti polymyositis-scleroderma antibody; Anti-Ro: SSA antibody; Anti-La: SSB antibody; PL-12: Anti alanyl-tRNA synthetase antibody*

The Figure showed distribution of ILD patterns varied across different connective tissue diseases (CTDs). Non-specific interstitial pneumonia (NSIP) emerged as the predominant pattern across all CTD subtypes that is 107(61.5%).

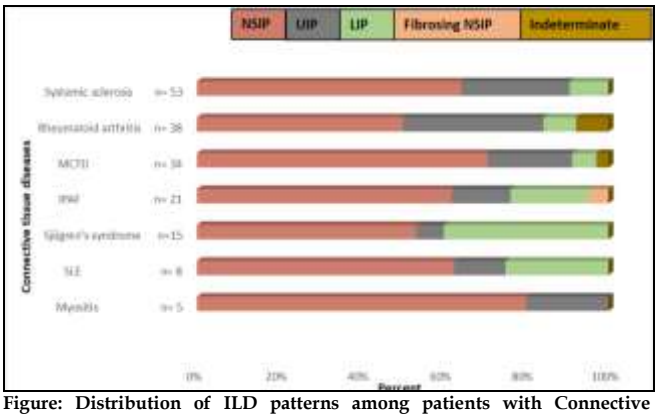

Figure: Distribution of ILD patterns among patients with Connective Tissue Disease

Table-II highlights the serological profiles observed among various CTD-ILD subtypes. ANA positivity was most frequently seen in patients with MCTD, Myositis, SLE, and Systemic Sclerosis (SSc), with positivity rates reaching 100% in the first three and 92.5% in SSc, indicating a strong diagnostic association. Anti-Ro/La antibodies were predominantly found in patients with Sjögren's syndrome (93.3%), consistent with its classical serologic pattern, and were also observed in some MCTD and IPAF patients. Overall, most serological differences were statistically significant ($p < 0.001$), emphasizing the diagnostic relevance of these markers in differentiating CTD-ILD subtypes.

Table-III summarized the clinical outcomes of ILD in various CTDs, showing considerable heterogeneity. The physician global assessment indicated that active disease was most common in SLE (62.5%), SSc (47.2%), and IPAF (38.1%), while MCTD and RA patients largely remained stable (70.6% and 60.5%, respectively). Worsening disease and deaths were more frequently noted in patients with SSc, Myositis, and Sjögren's syndrome. Although the difference in disease activity did not reach statistical significance ($p = 0.06$), the trend reflects variation in disease course among CTDs. This difference in pulmonary function was statistically significant ($p < 0.001$), underscoring the variable extent of lung involvement across CTDs. Collectively, these findings suggest that serological markers and PFTs are valuable tools in evaluating disease burden and predicting outcomes in CTD-associated ILD.

Table-II: Classification of CTD-ILD on the Basis of Serological Tests (n= 174)

Variables		SSc (n=53) n (%)	RA (n=38) n (%)	MCTD (n=34) n (%)	Myositis (n=5) n (%)	SLE (n=8) n (%)	Sjögren's syndrome (n=15) n (%)	IPAF (n=21) n (%)	*p*-value*
ANA	Positive	49 (92.5%)	5 (13.2%)	34 (100%)	5 (100%)	8 (100%)	14 (93.3%)	13 (61.9%)	<0.001
	Negative	2 (3.8%)	19 (50%)	0 (0)	0 (0)	0 (0)	1 (6.7%)	8 (38.1%)	
PM-Scl	Positive	1 (1.9%)	0 (0)	1 (2.9%)	0 (0)	0 (0)	0 (0)	2 (9.5%)	0.569
	Negative	50 (94.3%)	22 (57.9%)	33 (97.1%)	5 (100%)	8 (100%)	15 (100%)	19 (90.5%)	
Anti-Ro Anti-La	Positive	7 (13.2%)	1 (2.6%)	9 (26.5%)	1 (20%)	2 (25%)	14 (93.3%)	7 (33.3%)	<0.001
	Negative	43 (81.1%)	20 (52.6%)	25 (73.5%)	4 (80%)	6 (75%)	1 (6.7%)	14 (66.7%)	
PL-12	Positive	0 (0)	0 (0)	1 (2.9%)	1 (20%)	0 (0)	0 (0)	2 (9.5%)	0.005
	Negative	50 (94.3%)	21 (55.3%)	33 (97.1%)	4 (80%)	8 (100%)	15 (100%)	16 (76.2%)	
Anti-Scl- 70	Positive	29 (54.7%)	0 (0)	5 (14.7%)	0 (0)	0 (0)	1 (6.7%)	0 (0)	<0.001
	Negative	20 (37.3%)	22 (57.9%)	28 (82.4%)	5 (100%)	8 (100%)	14 (93.3%)	21 (100%)	
Anti-Sm	Positive	0 (0)	0 (0)	0 (0)	0 (0)	2 (25%)	0 (0)	0 (0)	0.003
	Negative	49 (92.5%)	18 (47.4%)	34 (100%)	5 (100%)	6 (75%)	15 (100%)	21 (100%)	
Anti-ds DNA	Positive	2 (3.8%)	0 (0)	2 (5.9%)	0 (0)	7 (87.5%)	1 (6.7%)	0 (0)	<0.001
	Negative	47 (88.7%)	21 (55.3%)	32 (94.1%)	5 (100%)	1 (12.5%)	14 (93.3%)	21 (100%)	
Anti-Ku	Positive	1 (1.9%)	0 (0)	3 (8.8%)	0 (0)	0 (0)	0 (0)	1 (4.8%)	0.630
	Negative	48 (90.6%)	21 (55.3%)	31 (91.2%)	5 (100%)	8 (100%)	15 (100%)	20 (95.2%)	
Anti-RNP	Positive	3 (5.7%)	0 (0)	21 (61.8%)	0 (0)	1 (12.5%)	1 (6.7%)	1 (4.8%)	<0.001
	Negative	44 (83%)	21 (55.3%)	13 (38.2%)	5 (100%)	7 (87.5%)	14 (93.3%)	20 (95.2%)	
Anti-Mi2	Positive	0 (0)	0 (0)	1 (2.9%)	0 (0)	0 (0)	0 (0)	1 (4.8%)	0.797
	Negative	48 (90.6%)	21 (55.3%)	32 (94.1%)	5 (100%)	8 (100%)	15 (100%)	20 (95.2%)	

**Fisher's Exact test, ANA: Antinuclear antibody; PM-Scl: Anti polymyositis-scleroderma antibody; Anti-Ro: SSA antibody; Anti-La: SSB antibody; PL-12: Anti alanyl-tRNA synthetase antibody*

Table-III: Outcomes of ILD patterns stratified by Connective Tissue Disease (n= 174)

Outcomes		SSc n (%)	RA n (%)	MCTD n (%)	Myositis n (%)	SLE n (%)	Sjögren's syndrome n (%)	IPAF n (%)	*p*-value*
Disease outcome as per physician global assessment	Active	25 (47.2%)	12 (31.6%)	8 (23.5%)	1 (20%)	5 (62.5%)	4 (26.7%)	8 (38.1%)	0.064
	Stable	20 (37.7%)	23 (60.5%)	24 (70.6%)	2 (40%)	3 (37.5%)	8 (53.3%)	8 (38.1%)	
	Worsening	5 (9.4%)	2 (5.3%)	2 (5.9%)	2 (40%)	0 (0)	1 (6.7%)	3 (14.3%)	
	Death	3 (5.7%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3%)	1 (4.8%)	
Hospitalization for exacerbation of ILD	Worsening	5 (9.4%)	1 (2.6%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.343
	Primary disease	43 (81.1%)	21 (55.3%)	33 (97.1%)	4 (80%)	8 (100%)	15 (100%)	19 (90.5%)	
	Infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
PFTs	Normal	1 (1.9%)	12 (31.6%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8%)	<0.001
	Mild restriction	10 (18.9%)	5 (13.2%)	6 (17.6%)	2 (40%)	2 (25%)	3 (30%)	3 (14.3%)	
	Moderate restriction	31 (58.5%)	12 (31.6%)	22 (64.7%)	0 (0)	5 (62.5%)	8 (53.3%)	9 (42.9%)	
	Severe restriction	11 (20.8%)	5 (13.2%)	6 (17.6%)	3 (60%)	1 (12.5%)	4 (26.7%)	4 (19%)	

**Fisher's Exact test, ILD: Interstitial lung disease; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; MCTD: Mixed connective tissue disease, SLE: Systemic lupus erythematosus; IPAF: Interstitial pneumonia with autoimmune features; PFT: Pulmonary function test*

DISCUSSION

This study evaluated the spectrum of ILD patterns in patients with connective tissue diseases at a tertiary care hospital in Lahore, Pakistan. Systemic sclerosis was found to be the most common CTD associated with ILD, and NSIP was the predominant HRCT pattern. ANA positivity was highly prevalent, while serological differences across CTDs were significant. Pulmonary function tests revealed moderate to severe restriction in a majority of patients.

In this study, the average age of participants was 49.4±13.7 years, with the largest proportion (36.8%) falling within the 46-60-year age group. Comparable findings were reported by Hazarika et al., who observed a mean age of 50.6 years, with 54% of participants aged over 50 10. Similarly, Ahmad et al. noted a mean participant age of 51.51±12.3 years, with a majority being older than 50 11. However, Lim et al. reported a significantly higher mean age of 67.9 years [12], while Karampeli et al. found a mean age of 63.2 years [13], both higher than what was observed in our study. The increased prevalence of autoimmune-related interstitial lung disease in older populations may be linked to decline in immune function with age, as well as cumulative exposure to infectious agents and environmental triggers that can initiate autoimmune responses [14].

CTD-ILD was found to be significantly more prevalent in females (93.7%) than males (6.3), resulting

in F/M ratio of 14.8:1 in present study. This finding is consistent with that of Zubairi and his coworkers who reported a female predominance of 90.1% in a CTD-ILD cohort (n=121) [15]. Similarly, Avala *et al.*[16] and Hazarika et al.10 observed higher proportions of female participants, at 86.67% and 83%, respectively. When compared with earlier studies by Jafri *et al.* (78.3%) 7, Lu *et al*. (74.5%) 17, Zubairi *et al*. (74.1%) 3, and Chartrand *et al*. (71.4%) 18, our results indicate a substantially higher female predominance. The greater prevalence of CTD-ILD in females may be explained by several factors, including genetic predisposition, the modulatory effects of endogenous hormones [18], as well as environmental and lifestyle influences [19].

Systemic sclerosis (30.5%) emerged as the most prevalent connective tissue disease, followed by rheumatoid arthritis (21.8%) in present research. The most frequently observed HRCT pattern was NSIP, seen in 61.5% of patients. These findings are consistent with the study by Vahidy et al., where NSIP was the predominant HRCT pattern in 42.1% of cases, followed by UIP in 15.8% [20]. In contrast, Zubairi and colleagues identified rheumatoid arthritis (42.3%) as the most common CTD in CTD-ILD patients, followed by systemic sclerosis (25%). Although NSIP remained the most frequent radiological pattern overall, patients with RA-ILD and systemic sclerosis were more likely to exhibit UIP features on HRCT. Similarly, Seetha et al. reported rheumatoid arthritis as the leading CTD, followed by systemic sclerosis, with UIP being the predominant HRCT pattern (30%), and followed by NSIP (27%) [21]. In a larger study by Vivero et al., among 381 patients, 325 (85.1%) were diagnosed with CTD-ILD, with rheumatoid arthritis, systemic sclerosis, and dermatomyositis accounting for 31%, 29%, and 15% of cases, respectively, while 36 patients (9.5%) met criteria for interstitial pneumonia with autoimmune features (IPAF) [22]. Variations in study findings may stem from factors such as differences in imaging quality, the presence of artifacts, extra-pulmonary manifestations, or variability in radiologist interpretation.

In this cohort, serological testing revealed a high prevalence of ANA positivity, observed in 73.6% of patients, which is comparable to the findings by Atienza-Mateo *et al.*[14] and Oliveira *et al.*[23] who reported ANA positivity in 71.1% and 79% of their patients. The presence of ANA in individuals with ILD, particularly when an underlying autoimmune disease is suspected, holds a high positive predictive value for diagnosing a rheumatologic condition. Among specific autoantibodies, anti-Ro/SSA and anti-La/SSB were detected in 23.6% of patients, highlighting their important role in the pathogenesis of ILD. This is in line with study of Nayebirad *et al.*[24] wherein it is demonstrated that anti-Ro52 (a subtype of anti-Ro/SSA) is associated with increased ILD prevalence and worse outcomes across a range of CTDs, including systemic sclerosis, Sjögren's syndrome, and IIM. Anti-Scl-70 antibodies were present in 20.1% of patients, reflecting their well-established association with fibrosing ILD in systemic sclerosis, where they are considered markers of more aggressive pulmonary involvement [14]. Additionally, anti-RNP antibodies were identified in 15.5% of patients, consistent with their known presence in MCTD and overlap syndromes, particularly those with ILD and mild myositis. Overall, these serological findings support existing evidence that antibodies such as anti-Ro/SSA, anti-La/SSB, anti-Scl-70, and anti-RNP serve not only as markers of systemic autoimmune disease but also as key predictors of ILD development and severity in patients with CTDs.

LIMITATION OF THE STUDY

Like other studies, this study has also limitations. Firstly, the retrospective design and single tertiary referral center limited ability of this study to draw and generalize findings to the broader population, potentially introducing selection bias. Lastly, the lack of long-term follow-up data restricted the evaluation of disease progression and treatment outcomes over time.

CONCLUSION

Non-specific interstitial pneumonia (NSIP) is the most prevalent radiological pattern among other ILD patterns. Systemic sclerosis emerged as the most frequent CTD associated with ILD in present cohort. Significant associations were observed between CTD subtypes and specific serological markers, radiological patterns, and pulmonary function outcomes. Our Study highlights the need for optimized treatment strategies as half of the patients in our cohort had active disease as per physician global assessment.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AL & MAS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MRH & MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

UA & HS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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