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Study of the Pulmonary Manifestations in Patients with Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis is a chronic inflammatory systemic disease which is variable in its effects. Although joint disease is the main presentation, there are a number of extra- articular manifestations including subcutaneous nodule formation, vasculitis, inflammatory eye disease and lung disease. ILD is the most common pulmonary manifestation of rheumatoid arthritis lung disease. Our purpose of the study was to assess the pulmonary manifestations of rheumatoid arthritis and its associated risk factors.

Materials and Methods: A cross sectional study was conducted in the Postgraduate Department of Medicine at Government Medical College Jammu after obtaining ethical clearance during a period of 1 year. A total of 100 patients of Rheumatoid arthritis who met the ACR EULAR criteria were included. Patients were further evaluated for pulmonary manifestations by physiological (pulmonary function test) and radiological methods (chest X-ray, HRCT chest). Chi-square test was used for comparison of categorical variables. A p value of less than 0.05 was considered statistically significant

Results: Out of 100 studied patients, 34% had lung involvement. ILD was present in 34% patients on HRCT. ILD was the most common lung manifestation of RA. Lung involvement was twice more common in males as compared to females. Longer duration of illness had significant impact. The other risk factors which were found significant in our study were smoking (p=0.002), clinically severe RA (p<0.001), high RF titres (p=0.009) and high anti CCP titres (p=0.004). UIP was the most common ILD seen in RA in our study.

Conclusion: In the present study conducted, there was high prevalence of pulmonary involvement as ILD in patients of rheumatoid arthritis. History of smoking, male sex, presence of rheumatoid factor, duration of illness and clinical severity of illness are all associated with progression to pulmonary involvement.

Keywords: Pulmonary, Rheumatoid Arthritis, Interstitial lung diseases

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory systemic disease which is variable in its effects but can progress swiftly to become severe and disabling in a short period of time. Rheumatoid arthritis affects ~1% of the population in developed countries. The incidence and prevalence of rheumatoid arthritis in developing countries is thought to be lower, but is difficult to quantify. [(1,2)] Although joint disease is the main presentation, there are a number of extra- articular manifestations including subcutaneous nodule formation, vasculitis, inflammatory eye disease and lung disease. [(3,4)] Of these manifestations, lung disease is a major contributor to morbidity and mortality.

Types of Pulmonary Involvement

Respiratory symptoms in rheumatoid arthritis can be due to a variety of conditions that affect the parenchyma [Interstitial lung disease (i.e. usual interstitial pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage and organising pneumonia], pleural[pleural effusion, Pneumothorax,

Bronchopleural fistula, Trapped lung syndrome], airways[Bronchiectasis, Follicular bronchiolitis, Obliterative (constrictive) bronchiolitis] Nodules [Rheumatoid nodules, Caplan syndrome] or vasculature [Rheumatoid vasculitis, pulmonary hypertension]. [5] The majority of respiratory manifestations occur within the first 5 years of disease. [6] Respiratory symptoms may precede onset of articular symptoms in 10–20% of cases. [7]

Interstitial lung disease

ILD is the most common pulmonary manifestation of rheumatoid arthritis lung disease. [8] In an Australian cohort of rheumatoid arthritis patients with a disease duration<2 years, 58% of these patients had changes consistent with ILD on either chest radiograph, High-resolution computed tomography (HRCT), pulmonary function testing (PFT), bronchoalveolar lavage (BAL).Of these patients, 76% had clinically silent disease. [9] It is currently estimated that ∼30% of patients with rheumatoid arthritis have subclinical ILD noted on HRCT scans. [8]

Epidemiology/risk factors

Although rheumatoid arthritis is more common in females, rheumatoid arthritis associated-ILD (RA-ILD) occurs more frequently in males, with a male to female ratio as high as 2:1 in some studies. [10,11] Onset of lung disease typically occurs in the fifth to sixth decade of life. [12] Age has consistently been shown to be a risk factor for the development of ILD. [13] Another major risk factor is a history of smoking, with one study finding an odds ratio of 3.8 for those who smoked >25 pack-years. [14] High levels of rheumatoid factor are a known risk factor involving formation of circulating immune complexes. [15]

Pathogenesis

The mechanism of pulmonary fibrosis occurring in ILD is not well understood. Patients with rheumatoid arthritis typically have circulating autoantibodies, the most common being rheumatoid factor and anti-cyclic citrullinated peptide (CCP). [16] Anti-CCP antibodies have also been associated with the development of airway disease. [17]

Cigarette smoking may play a role in inducing antibody formation and has been linked to higher titres of rheumatoid factor. [14] Smoking may promote citrullination of lung proteins, thus leading to the development of anti-CCP antibodies.

Pulmonary function tests

The majority of patients with RA-ILD will have a restrictive pattern on PFTs, with or without decreased diffusing capacity of the lung for carbon monoxide (DLCO) and hypoxemia. [10] Impairment of both forced vital capacity (FVC) and DLCO is associated with poorer prognosis. Airflow obstruction may coexist and be seen in patients manifesting airway involvement, i.e. bronchiolitis obliterans.

Imaging

In UIP, HRCT scans show subpleural, basal predominant, reticular abnormalities with honeycombing, and traction bronchiectasis but a relative absence of ground-glass opacities. [18] NSIP is the second most common pattern, occurring in ∼11–32% of patients. NSIP is characterised by basilar predominant ground-glass opacities and absence of honeycombing. Additional patterns less commonly seen in rheumatoid arthritis include other patterns of interstitial pneumonia, including organising pneumonia, diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP)-like patterns. [19]

Prognosis

ILD is second only to cardiac disease as a cause of mortality in rheumatoid arthritis [6,10,11] The mean survival for RA-ILD overall has been estimated at 2.6 years from time of diagnosis compared to 9.9 years for rheumatoid arthritis patients without lung involvement; however, this probably reflects the predominance of the UIP pattern. [12]

Pleural disease

Pleural involvement is a common pulmonary manifestation of rheumatoid arthritis, with small pleural effusions noted in up to 70% on autopsy studies. However, only about 3–5% of patients are symptomatic. Most effusions are unilateral, although occasionally bilateral effusions are found. Fever and pleuritic chest pain are common, but cough is generally absent unless there is comorbid parenchymal lung disease.

Lower airway involvement

Lower airway disease may include bronchial hyperresponsiveness, bronchiolitis or bronchiectasis. Similar to RA-ILD, estimates of the prevalence of obstructive airway disease are highly variable depending on the criteria used to define disease and the population studied. [(20)]

Follicular bronchiolitis occurs in the setting of hyperplasia of BALT.HRCT demonstrates centrilobular peri bronchial nodules <3 mm in size with branching structures corresponding to bronchial dilation and wall thickening.

Obliterative bronchiolitis is a more severe and often fatal condition characterised by progressive narrowing of the bronchioles. HRCT findings are nonspecific, but may show centrilobular emphysema, bronchiectasis, bronchial wall thickening or mosaic attenuation. PFTs generally show airflow obstruction with a normal DLCO.

Bronchiectasis has been demonstrated on HRCT in ~30% of cases of rheumatoid arthritis, although it may be clinically silent. [(21)] Among patients with rheumatoid arthritis and bronchiectasis, mortality rates are higher than for either condition alone

Pulmonary nodules

Rheumatoid nodules can occur in the lungs, particularly in patients with longstanding disease and subcutaneous nodules. Uncomplicated nodules may spontaneously regress or improve with standard rheumatoid arthritis therapy.

A rare complication known as Caplan syndrome (also known as rheumatoid pneumoconiosis) may occur in those with pneumoconiosis from occupational exposure to coal, silica or asbestos. Patients with this syndrome are often asymptomatic and the overall prognosis is good. Complications occur when lesion cavitates and becomes infected or ruptures into the pleural space.

Our purpose of the study was

i. To study the pulmonary manifestations of rheumatoid arthritis by clinical, radiological and physiological methods.
ii. To identify the association between lung manifestations & duration of disease.
iii. To study the risk factors that contributes to pulmonary involvement in rheumatoid arthritis

METHODOLOGY

A cross sectional study conducted in the Postgraduate Department of Medicine at Government Medical College Jammu after obtaining ethical clearance during a period of 1 year from Nov 2017 to Nov 2018. A total of 100 patients of Rheumatoid arthritis of either sex having age >21 years who met the ACR EULAR (2010) criteria for RA were included. [(1)] Patients with history of obstructive lung disease, cardiopulmonary disorder, collagen vascular disease (SLE, scleroderma), viral infection (hepatitis B & C, HIV), tuberculosis and inhalational exposure / occupational lung disease (asbestos, silica) were excluded.

Detailed history regarding duration of illness and various risk factors like smoking, gender, age, high RF titres (>3x ULN) and high anti CCP titres (>3x ULN), and clinically severity of disease (as per Clinical Disease Activity Index-CDAI) was taken. Patients were examined clinically for respiratory signs and symptoms. Patients were further evaluated for pulmonary manifestations by physiological (pulmonary function test) and radiological methods (chest X-ray, HRCT chest).

In patients with clinical suspicion of tuberculosis sputum for AFB was done for

exclusion of pulmonary tuberculosis. Patients with evidence of pulmonary fibrosis on HRCT chest were further investigated for HBsAg, anti-HCV, HIV to rule out pulmonary fibrosis secondary to viral infections. Majority of our patients were on DMARDs and were not excluded from our study.

STATISTICAL ANALYSIS:

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0. Continuous variables were expressed as Mean±SD and categorical variables were summarized as percentages. Chi-square test was used for comparison of categorical variables. Graphically the data was presented by bar and pie diagrams. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 100 patients of rheumatoid arthritis were studied. Baseline characteristics showed that 9% of patients were in age group of 21-30 years, 23% in age group of 31-40 years, 23% in age group of 41-50 years, 21% in age group of 51-60 years and 24 % in age group of > 60 years. Of these 24% were males and 76% were females, female to male ratio was 3.2:1. The duration of illness was < 5 years in 40% patients, 6-10 years in 38% patients, 11-15 years in 14% patients and > 15 years in 8 % patients.

Smoking was present in 30% of patients, male gender in 24% of patients, high RF titres was present in 60% of patients, high anti CCP titres was present in 50% of patients, advanced age was present in 25% of patients and clinically severe RA was present in 21% of patients.

Chest X-Ray findings was normal in 74 % patients and abnormal in 16% patients. Reticulonodular pattern was seen in 16 %, bilateral lower zone haziness seen in 9% patients and prominent vascular markings in 3 % of patients. PFT was normal in 63% of patients. Restrictive pattern was seen in 20 % of patients, obstructive pattern was seen in 9 % of patients, and 8 % patients were not cooperative for PFT.HRCT was normal in 57 % patients. Reticulations were present in 14% of patients, honey combing was present in 19 % of patients, ground glass opacities in 16%, pleural thickening in 8 %, pleural effusion in 3 %, pulmonary vascular prominence in 5%, rheumatoid nodules in 6%, emphysematous changes in 1% and bronchiectasis in 4%.

Table1: Age distribution of study patients

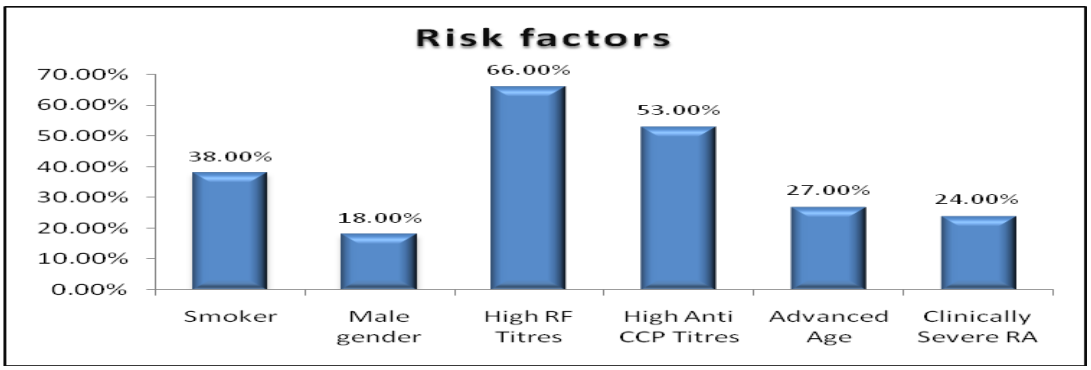
Age (years)	No. of patients	Percentage
21-30	9	9%
31-40	23	23%
41-50	23	23%
51-60	21	21%
> 60	24	24%
Total	100	100%
Mean ± SD = 49.5 ± 13.51		

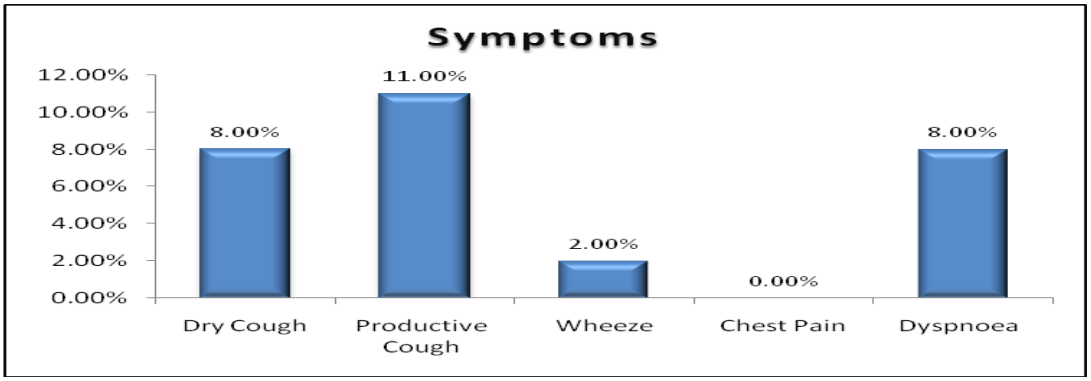
Table2: Gender distribution of study patients

Gender	No. of patients	Percentage
Male	18	18%
Female	82	82%
Total	100	100%
Female : Male = 3.2:1		

Table 3: Distribution of study patients as per duration of illness (RA)

Duration (years)	No. of patients	Percentage
≤ 5	36	36%
6-10	36	36%
11-15	17	17%
> 15	11	11%
Total	100	100 %





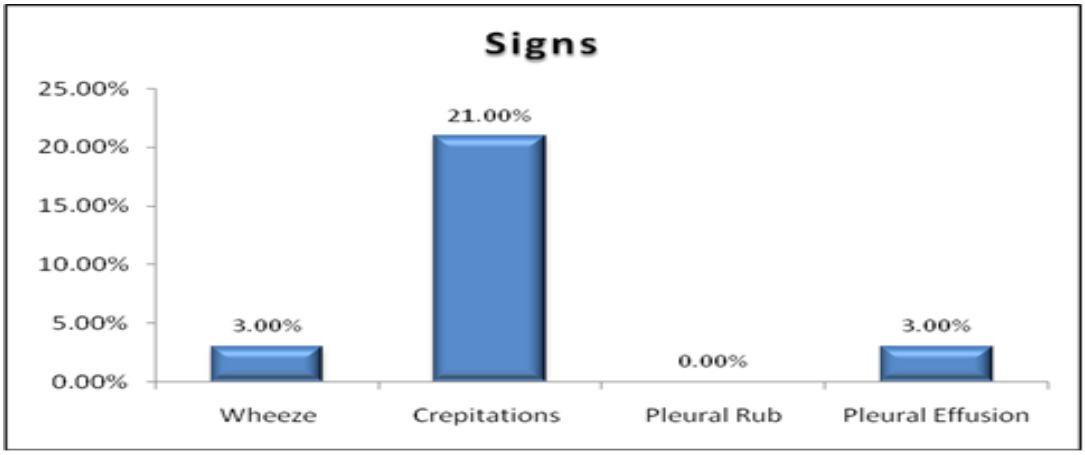


Table 4: Distribution of Study patients as per Chest X-Ray findings

Chest X-Ray Findings	No. of patients	Percentage
Normal	74	74%
Reticulonodular Pattern	16	16%
Prominent Vascular Markings	3	3%
Bilateral Lower zone Haziness	9	9%

Table 5: Distribution of Study patients as per pulmonary function test

PFT	No. of patients	Percentage
Normal	63	63%
Restrictive	21	21%
Obstructive	8	8%
Not Cooperative	8	8%

Table 6: Distribution of study patients as per HRCT Pattern

Signs	No. of patients	Percentage
Normal	58	58%
Reticulation	13	13%
Honey Combing	18	18%
Ground Glass Opacities	15	15%
Pleural Thickening	9	9%
Pleural Effusion	4	4%
Pulmonary Vascular Prominence	5	5%
Rheumatoid Nodules	6	6%
Emphysematous changes	1	1%
Bronchiectasis	4	4%

Age distribution of RA-ILD patients shows that 7.1% of patients were in 31-40 years of age group, 25% of patients were in 41-50 years of age group, 39.3% of patients were in51-60 years of age group and 28.6% of patients were in > 60 years of age.

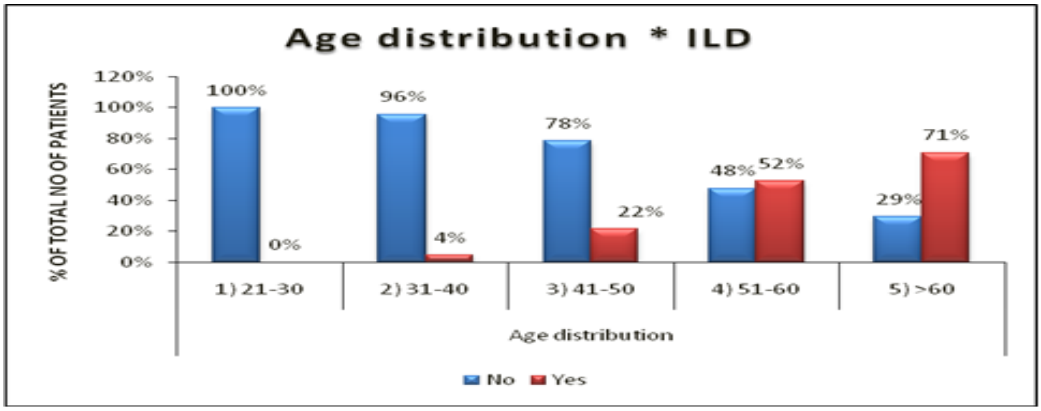
The number of patients with ILD increases with increase in duration of illness. 3 (6.98%) patients had < 5 years, 9 (25%) patients had 6-10 years, 10 (76.92%) patients had 11-15 years, and 6 (75%) patients had > 15 years of illness.

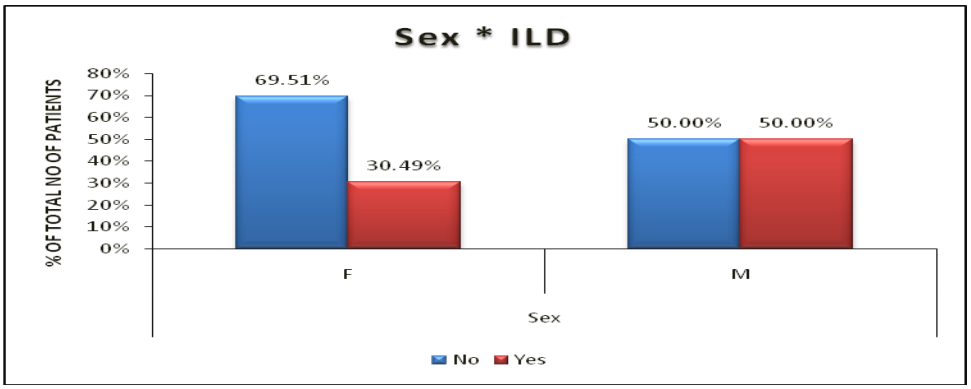
Among the various risk factors associated with RA-ILD patients, the association between (smoking, male gender, high RF titres, high anti CCP titres, advanced age, clinically severe RA) and RA ILD was significant with p=0.002, p=0.026, p=0.009, p=0.004, p<0.001 and p<0.001 respectively.

Chest X Ray was normal in 28.6% of patients, reticulonodular pattern in 39.3% of patients, prominent vascular makings in 7.1% of patients and bilateral lower zone haziness in 32.1% of patients.

PFT was normal in 28.6% of patients, restrictive pattern was seen in 50% of patients, obstructive pattern was seen in 7.1% of patients and 14.3% of patients were not cooperative for PFT. As per HRCT

Pattern. Reticulations were present in 35.7% of patients: honey combing was present in 53.6% of patients, ground glass opacities in 42.9%, pleural thickening in 10.7%, pleural effusion in 7.1%, pulmonary vascular prominence in 7.1%, rheumatoid nodules in 7.1% and bronchiectasis in 7.1%.





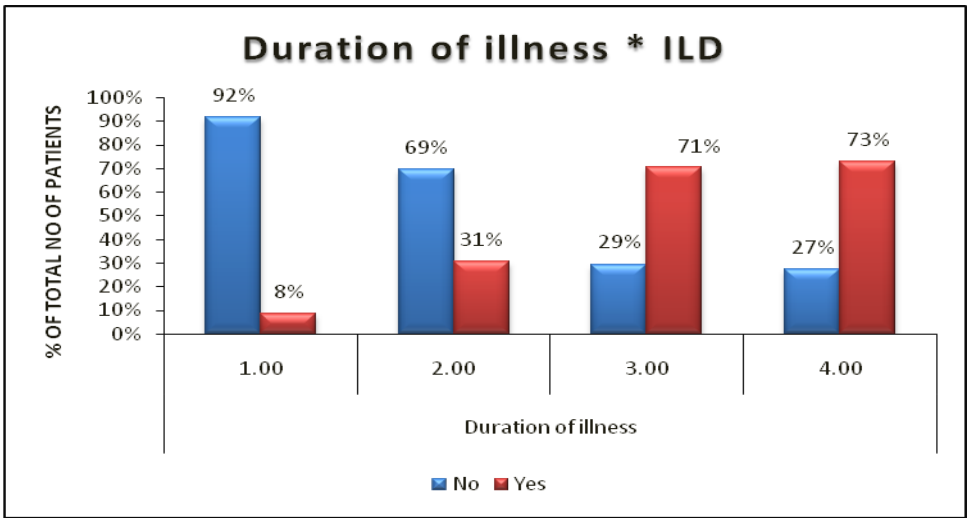
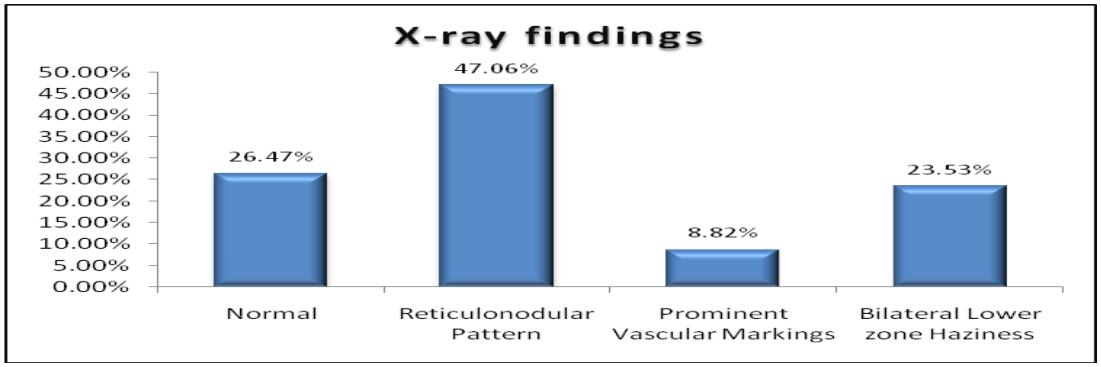


Table 7: Risk factors associated with RA-I LD patients

Risk Factor	RA-ILD Patients		Control RA Patients without ILD		P-value
	No.	%age	No.	%age	
Smoker	22	53.6	15	20.8	0.002*
Male Gender	9	39.3	13	18.1	0.026*
High RF titre	29	82.1	37	51.4	0.009*
High Anti CCP titre	26	75.0	29	40.3	0.004*
Advanced Age	18	39.3	14	19.4	<0.001*
Clinically Severe RA	20	57.1	5	6.9	<0.001*

Table 8: Showing symptoms among RA-ILD patients		
Symptoms	No. of patients	Percentage
Asymptomatic	11	39.3%
Dry Cough	7	25.0%
Productive cough	6	21.4%
Wheeze	1	3.6%
Chest Pain	0	0.0%
Dyspnoea	3	10.7%

Table 9: Showing various signs among RA-ILD patients		
Signs	No. of patients	Percentage
No signs	6	21.4%
Wheeze	2	7.1%
Crepitations	18	64.3%
Pleural Rub	0	0.0%
Pleural Effusion	2	7.1%



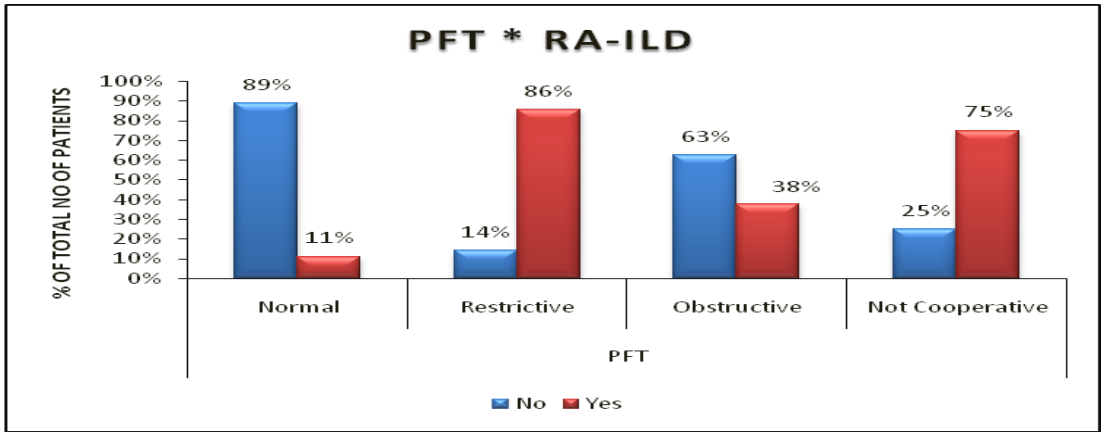


Table 10: Distribution of RA-ILD patients as per HRCT Pattern		
HRCT Pattern	No. of patients	Percentage
Reticulation	10	35.7%
Honey Combing	15	53.6%
Ground Glass opacities	12	42.9%
Pleural Thickening	3	10.7%
Pleural Effusion	2	7.1%
Pulmonary Vascular Prominence	2	7.1%
Rheumatoid Nodules	2	7.1%
Emphysematous Changes	0	0.0%
Bronchiectasis	2	7.1%

Table 11: Distribution of RA-ILD patients as per HRCT Pattern				
Type of ILD	Males	Percentage	Females	Percentage
UIP	7	72.73	13	47.06
NSIP	2	27.27	12	52.94
Total	9	100	25	100

Table 12 Gender distribution in relation with RA-ILD			
		No. of patients	Percentage
Male	With ILD	9	45.8
	Without ILD	9	54.2
Female	With ILD	25	22.4
	Without ILD	57	77.6

Among the patients with RA-ILD, 72.73% of males had UIP while 47.06% of females had UIP and 27.27% of males had NSIP while 52.94% of females had NSIP. A total of 45.8% of males and 22.4% of females had ILD, male to female ratio 2:04

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DISCUSSION

Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5-1% of the world population. Being a multisystem disorder, RA virtually affects every organ system of the body and one of the major causes of mortality in patients of RA is lung involvement, cardiovascular involvement being most important cause.

Out of 100 studied patients, 34% had lung involvement. ILD was present in 34% patients on HRCT. ILD was the most common lung manifestation of RA, other

lung manifestations being pleural thickening, pleural effusion, rheumatoid nodules, bronchiectasis, emphysematous changes and prominent pulmonary vasculature. In the study done by Gobbay E et al. (1997) RA-ILD was seen in 33% on HRCT. [(9)] Similar results were demonstrated by Gochuico BR et al. (2008). [(22)]

The mean age at detection of ILD was 56.1±9.77, higher than mean age of studied RA patients (49.5±13.51). Analysing the pattern of distribution of age in RA patients with and without lung involvement, the lung involvement increased proportionately as the age advanced. The percentage of patients with lung involvement in age group > 60 years dropped to 28.6% as compared to 39.3% in age of 51-60 years. The lesser proportion of patients in age more than 60 years can be attributed to higher mortality of RA in this age group, but further studies are needed to validate our assumption. The results in our study were in comparison with the study conducted by Kelly et al. (2014) who demonstrated that median age at diagnosis of RA was 56 years (range 23-76). [(16)] Similarly Assayag D et al. (2014) , studies mean age ranged 55 to 69 years in RA-ILD. [(13)] Our findings were also consistent with study done by Bilgici A et al. (2005). [(23)]

Though females outnumbered males by a ratio of 3.2:1 as is characteristic of autoimmune disorder, once gender comparison of RA patients was done. But lung involvement was twice more common in males as compared to females. The results of our studies are validated by the study conducted by De Lauretis et al. (2011) where in his study ILD has affected men twice as commonly as women. [(11)] Duration of illness in our study had a marked impact over the progression of lung involvement in patients of RA. The magnitude of lung involvement increased threefold once the patients with disease duration 6-10 years (25%) were compared to patients with disease during of 11-15 years and >15 years (76.92% and 75% respectively). Longer duration of illness had significant impact in lung involvement in study conducted by Shunsuke Mori et al. (2012) [(20)]

The other risk factors which were found significant in our study were smoking (p=0.002), clinically severe RA (p<0.001), high RF titres (p=0.009) and high anti CCP titres (p=0.004). The results of our study can be translated into a fact that early lung screening may be warranted in smokers and with clinically severe disease. These results were consistent with the study done by Shunsuke Mori et al. (2012), who found that ILD was more often seen in smokers (45.8%), in male patients (50%), those with high titres of RF (70.8%), those with high titres of anti-CCP (79.2%), the median age of the ILD group was significantly older than that of the patients without pulmonary complications (p < 0.0005). [(20)] In another study done by Kelly et al. (2014), 67% of patients with RA-ILD were smokers and titres of Anti-CCP were significantly higher in patients with RA-ILD. [(16)] Similarly, another study reported male gender as a risk factor for RA-ILD (p <0.04). [(9)] Bilgici A, et al. (2005) also studied that advanced age and clinically severe disease were significant risk factors for lung involvement (p <0.01 and p <0.01 respectively). [(23)]

Considering the symptomatology of RA with pulmonary involvement, cough was a more persistent symptom, involving about half of the patients with pulmonary involvement (dry cough in 25% and productive cough in 21.4%). Lung crepitations can be sign with high sensitivity used for the prediction of ILD in patients of RA as reflected by results of our study where lung crepitations were found in 64.3% of patients with ILD. Similar results were seen by N. Fatima et al. (2013). [(24)]

Chest X ray being the primary imaging modality for screening of lung pathology revealed abnormality in about three quarters of patients with reticulonodular pattern and lower lobe haziness in 39.3% and 32.1% of patients respectively. Similar findings were as demonstrated by N. Fatima et al. (2013)

who found that the predominant finding on chest X-ray was reticulonodular pattern. [(24)]

Sixteen (57.1%) patients had UIP with reticulation with or without honeycombing on HRCT and 12 (42.9%) patients had NSIP with predominant ground glass opacities on HRCT. UIP was the most common ILD seen in RA in our study. In the study done by De Lauretis et al (2011), NSIP was the most common pattern in all CTDs, except for RA which is characterized by a higher frequency of UIP. [(11)] Similarly, Kelly et al (2014) also studied that UIP was the most common subtype on HRCT. [(16)] UIP was predominantly seen in 65% followed by NSIP in 24%. In our study, second most common pattern was NSIP; Similar results were seen by Lee HK et al. (2005) [(27)] UIP was more common in males compared to NSIP as reported by similar studies. [(24-28)]

Pulmonary function test was abnormal in 16 (57.1%) patients with predominant restrictive pattern in 14 (50%) patients. In the study done by N. Fatima et al. (2013), 27 patients (43%) had abnormal PFT with restrictive pattern in 18 (29%) and obstructive pattern in 5 (8%) of patients. [(24)] In similar studies, restrictive pattern was seen in 52.9% and obstructive pattern in 11.8% of patients. [(29,30)]

About 34% had lung involvement of which majority of the patients had ILD. Stressing upon the fact, modifying risk factors like smoking, early recognition and treatment of RA can halt or modify lung involvement in RA. As the duration of illness increases, need for screening for pulmonary involvement with chest x ray and PFTs is to be emphasized along with periodic chest examination of patients with RA.

CONCLUSION

In the present study conducted, there was high prevalence of pulmonary involvement as ILD in patients of rheumatoid arthritis. The commonest type of ILD was UIP as compare to NSIP. History of smoking, male sex, presence of rheumatoid factor, duration of illness and clinical severity of illness are all associated with progression to pulmonary involvement.

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