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To Study Clinical And Radiological Profile Of Connective Tissue Disease Associated Interstitial Lung Disease.

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ABSTRACT :
INTRODUCTION: *Connective tissue disorders are a diverse group of immunologically mediated systemic disorders that are often associated with pulmonary manifestations. huge differences are present based on selection criteria regarding the respiratory involvement due to connective tissue diseases however increased mortality and morbidity develops due to pulmonary involvement due to connective diseases .*
AIMS AND OBJECTIVES
To study the clinical profile of CTD-ILD patients.
To study the radiological profile (Chest X-ray and HRCT scan) of CTD-ILD patients.
Study Design & Period:
Prospective observational study from September 2019 to November 2021.
Study Population:
30 patients of connective tissue disease associated interstitial lung disease who attended to Pulmonology department, Chalmeda medical college were included.
RESULTS: *The Mean age in the present study is 49.4 years.NSIP being the most common HRCT pattern,restrictive pattern was the most common spirometric pattern, PAH was the most common 2D-ECHO finding,*
CONCLUSION*:In the present study Systemic sclerosis was most commonly associated connective tissue disease associated interstitial lung disease followed by mixed connective tissue disease and rheumatoid arthritis*
KEYWORD : *Morning stiffness ,Ocular sicca, Fatigue, Raynauds phenomenon, Gastroesophageal reflux disease , Malar rash , Anti nuclear antibody.*

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I. INTRODUCTION

The pulmonary interstitium is the network of connective tissue fibres that supports the lung. It includes the alveolar walls, interlobular septa and the peri Broncho-vascular interstitium. **Interstitial lung diseases (ILD)** are a group of disorders that mainly affects these supporting structures. Although the majority of disorders(1) also involve the air spaces, the main abnormality is thickening of the interstitium which may be due to accumulation of fluid, cells or fibrous tissue. ILD are difficult to classify as approximately,150 plus known diseases are characterized by interstitial involvement either as a primary disease or as a part of multi-organ process as may occur in Connective Tissue Diseases (CTD)(12). The diagnostic strategy in a patient with ILD is based on the dynamic time course (acute, sub-acute, chronic), the cause (known or unknown) and the disease at presentation (presence of extra pulmonary / systemic disease manifestations).

Various classification schemes for ILD are proposed, which include histopathologic and clinical characteristics. The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus panel classification system was published in 2001 and has recently been revised. It is often helpful in the case of any individual patient to incorporate a combination of historical, clinical, radiographic, and pathologic features. Distinguishing those patients who have a known cause for their ILD (e.g., connective tissue disease, occupational or environmental exposure, or drug toxicity) from those who do not (e.g., Idiopathic Pulmonary Fibrosis, sarcoidosis) is an important first step. Clinical features, such as acuity of onset, may help to classify disease as well .(2)

Rheumatoid Arthritis (RA):

Reported incidence of RA ranges from 0.2 to 3 per 1000 person years (<0.5 per 1000 person years in most surveys) with a rising incidence with increasing age into the 7thdecade [1]. In adult whites prevalence ranges from 0.5 to 2 percent with a male to female ratio between 1:2 to 1:4[1]. Evidence in support of genetic predisposition includes familial and twin clustering and associations between RA and HLA-DRB1 alleles. Hormonal factors may play a role judging from the female preponderance.

Systemic Sclerosis:*Incidence is approximately 2- 20 per 1 lakh per year with a peak incidence in the 4th to 6th decades [1]. Prevalence is 30 to 120 per 1 lakh with 3:1to 8:1 female preponderance [1]associated with HLA-DR3, HLA-52A, HLA-DRB1*11 and HLA-DPB1*1301.*

Polymyositis (PM)/ Dermatomyositis (DM):*The inflammatory myopathies are relatively rare affecting 2 – 10 per 1 lakh population with a female to male preponderance of 2.5:1 with a Bimodal age distribution peaking in childhood and in the 4th to 5th decades [1]. DM appears to have higher expression of HLA-B8,HLA-DR3, HLA-B14, HLA-B40 whereas PM is associated with HLA B8/DR3 and in African Americans with HLA B7 and HLA-DRW6.*

Mixed Connective tissue disorder (MCTD):

Prevalence is unclear but it is estimated at 1 in 10000 with a 9:1 female preponderance most frequently presenting in 4th decade **[1]**.

Sjogren's Syndrome:

Prevalence ranges from 0.5 to 3% **[1]**. Evidence supporting genetic predisposition includes Familial Clustering and an association with HLA DW2 and HLA-DW3.The data about prevalence of CTD ILD were limited from India, the present study was an attempt in that direction.

AIMS AND OBJECTIVES

To study the clinical profile of CTD-ILD patients.
To study the radiological profile (Chest X-ray and HRCT scan) of CTD-ILD patients.

Study design & period:

Prospective observational study from September 2019 to November 2021.

Study population:

30 patients of connective tissue disease associated interstitial lung disease who attended to Pulmonology department, Chalmeda medical college were included

Inclusion criteria:

1. Previously diagnosed cases of connective tissue disease associated interstitial lung disease.
2. Patients should fulfill ACR criteria for Scleroderma/Rheumatoid arthritis/Sjogrens syndrome/Mixed connective tissue disease and antisynthetase syndrome with ILD will be included.
3. Connective tissue disease patients with velcro rales on respiratory system examination were further investigated and then included.

Exclusion criteria:

1. Patients with ILD with autoimmune features but not fulfilling CTD criteria.
2. Drug induced ILD.
3. Smoking induced ILD.
4. Interstitial lung disease mimicking like infections e.g. Miliary tuberculosis and Pneumocystis jirovecii pneumonia (PJP).
5. Interstitial lung disease like malignancies e.g. Lymphangitis carcinomatosis

All the 30 patients were thoroughly examined with respect to history, physical examination of all systems, radiological examination, Spirometry and Laboratory investigations. The history included symptoms like cough, shortness of breath, chest pain, reflux symptoms, dry eyes, dry mouth, Raynaud's phen Smoking history and Family history were taken in detail. Occupational history was noted.History of any exposure to birds like pigeons, doves, ducks, hens, were taken. Any history of drug intake was noted. arthralgia, redness and pain at the joint sites ,thorough Physical examination was done in all cases. Any positive findings like clubbing, peripheral lymphadenopathy, abnormal breath sounds and added sounds like Velcro crackles were noted. Examination of the cardiovascular system was, 2D-Echo was done in all cases Examination of the

musculoskeletal system was done for detecting any abnormal joint manifestations. Examination of the nervous system, eye and GIT were done to look for any co-existent abnormalities. A special emphasis was laid in the examination of the skin to look for any cutaneous manifestations like rashes, subcutaneous nodules, skin tightening, pigmentation ,nail ,and ,nailbed abnormalities Investigations:

Routine laboratory Investigations were done that include Hemoglobin (gm%), Total leukocyte and Differential leukocyte counts, serum creatinine, AEC, RBS, and a complete urine examination.Antibodies were done in whom these tests were not done previously,include Anti-Cyclic Citrullinated Peptide, Antinuclear Antibody, Anti Double-Stranded DNA, Rheumatoid Factor, Anti Ribo-nuclear Protein, Anti-Nuclear Ab, Anti-Scl70 Ab, Anti-Centromere Ab, Anti-Ro-Anti- La Ab, Anti-Smith Ab, Anti-Jo Ab and Anti-RNA Synthase Ab.A chest x-ray and a HRCT were done where it was not performed previously. Spirometry was done in all cases. The baseline SpO2 was recorded at rest.

Ethical issues:Informed consent was obtained,Confidentiality of individual's information was maintained,Subjects were given write to withdraw consent at any stage,No monetary or other additional benefits were given to the participants in this study.

II. RESULTS

Out of the 30 patients, most affected age group was 31 – 60. 83.3% were seen in that age group. Mean age was 49.4 years.

Table No. 1: Age and sex wise distribution of patients.

AGE and SEX WISE DISTRIBUTION			
AGE	**Males**	**Females**	**Mean Age**
< 20	**-**	**1**	**49.4 YEARS**
21 -30	**-**	**2**	
31 – 40	**-**	**8**	
41 – 50	**-**	**8**	
51 – 60	**1**	**9**	
> 60	**-**	**1**	

In the present study, out of 30 patients, only one (3.3%) was male and the remaining 29 (96.7%) were females.

Table No. 2: Sex wise distribution of patients

SEX DISTRIBUTION		
	Total	**Percentage**
MALES	**1**	**3.3%**
FEMALES	**29**	**96.7%**

In the present study, out of 30 patients, only 4 (13.3%) were smokers, and the remaining 26 (86.7%) were non-smokers.

Table No. 3: Smoking status of the patients.

SMOKING STATUS				
	Males	**Females**	**Total**	**Percentage**
SMOKERS	**1**	**3**	**4**	**13.3%**
NON-SMOKERS	**-**	**26**	**26**	**86.7%**

Most common clinical presentations were cough and shortness of breath, which were present in all (in 30 patients, 100%), followed by fatigue (in 25 patients, 83.3%), dryness of skin (in 19 patients, 63.3%), Raynaud's phenomenon (in 14 patients, 46.6%).

Table no : 4 tabular representation of the symptomatic profile

SYMPTOMATIC PROFILE				
	Males	**Females**	**Total**	**Percentage**
COUGH	**1**	**29**	**30**	**100%**
SHORTNESS OF BREATHE	**1**	**29**	**30**	**100%**

FATIGUE	**1**	**24**	**25**	**83.3%**
DRYNESS OF SKIN	**-**	**19**	**19**	**63.3%**
RAYNAUD'S	**-**	**14**	**14**	**46.6%**

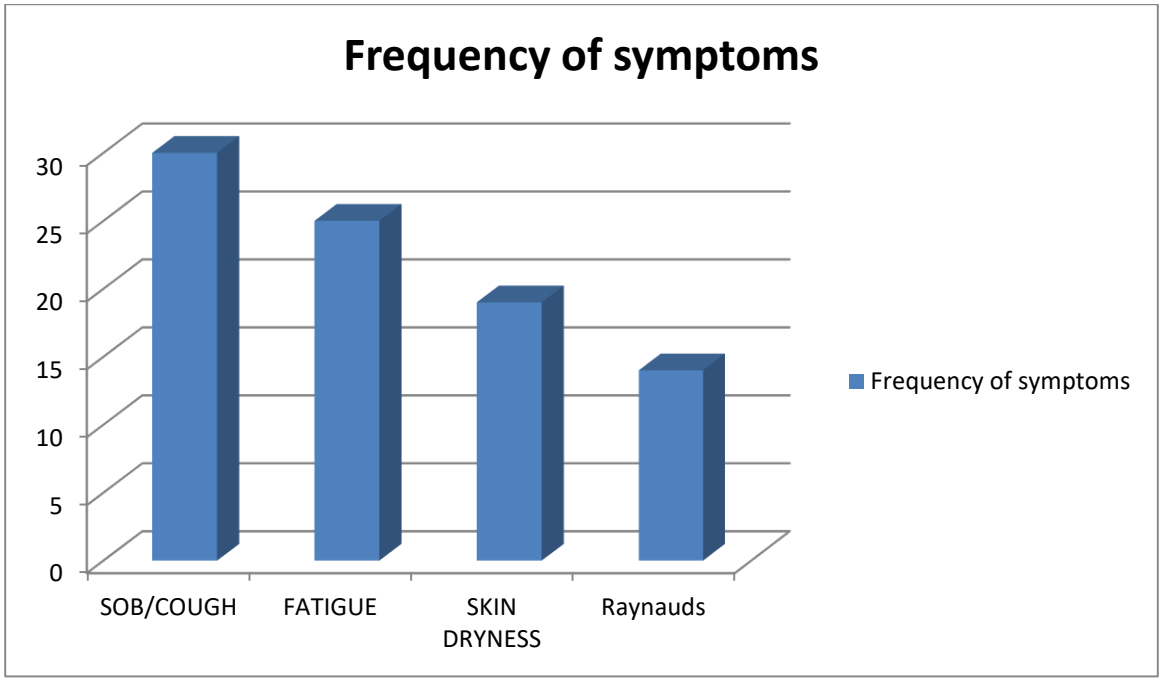

Figure 1.Graphical representation of symptomatic profile

Other symptoms in descending order include Joint pains (in 13 patients, 43.3%), Morning Stiffness (in 8 patients, 26.6%), Gastro-Esophageal Reflux Disease (in 7 patients, 23.3%), Dysphagia (in 7 patients, 23.3%) and Dryness of Mouth and eyes (in 1patient,3.3%)

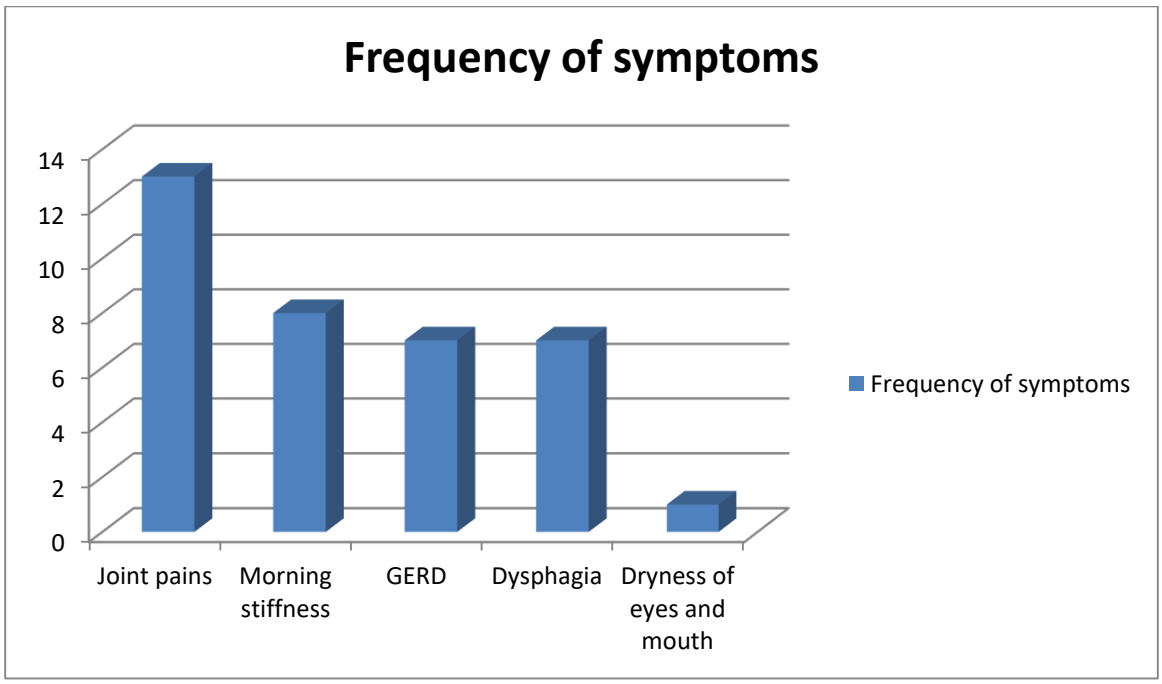

Figure 2.Graphical representation of symptomatic profile

Table No. 5: Tabular representation of the symptomatic profile.

SYMPTOMATIC PROFILE				
	Males	Females	Total	Percentage
JOINT PAINS	-	13	13	43.3%
MORNING STIFFNESS	-	8	8	26.6%
GERD	-	7	7	23.3%
DYSPHAGIA	-	7	7	23.3%
DRYNESS of EYES & MOUTH	-	1	1	3.3%

Most common Physical examination finding was pallor (in 26 patients, 86.6%). Other findings include clubbing (in 11 patients, 36.6%), skin thickening (in 11 patients, 36.6%), fish mouth (in 8 patients, 26.6%), joint deformities (in 7 patients, 23.3%). Malar rash was seen only in one patient (3.3%).

Table No. 6: Tabular representation of the Physical examination findings.

PHYSICAL EXAMINATION FINDINGS				
	Males	Females	Total	Percentage
PALLOR	1	25	26	86.6%
CLUBBING	1	10	11	36.6%
SKIN THICKENING	-	11	11	36.6%
FISH MOUTH	-	8	8	26.6%
JOINT DEFORMITIES	-	7	7	23.3%
MALAR RASH	1	-	1	3.3%

All the patients (in 30 patients, 100%) were found to have Velcro rales on auscultation of Lungs.

Table No. 7: Tabular representation of Respiratory system Auscultatory Findings

RESPIRATORY SYSTEM AUSCULTATORY FINDINGS				
	Males	Females	Total	Percentage
NORMAL	-	-	-	0%
VELCRO RALES	1	29	30	100%

Most of the patients (in 21 patients, 70%) were having a saturation of ≥ 93% with room air. Eight patients (26.7%) were having a saturation of ≤ 88% with room air. One patient (3.3%) was having a saturation level between 89% to 92%. Mean SpO2 was 92.5 ± 5.1.

Table No. 8: Tabular representation of Oxygen saturation.

OXYGEN SATURATION				
SpO2	Males	Females	Total	Percentage
≥ 93%	-	21	21	70%
89% – 92%	-	1	1	3.3%
≤ 88%	1	7	8	26.7%

Most common Chest X-ray findings in the present study were bilateral basal reticular pattern (in 30 patients,100%) and Reduced lung volumes (in 30 patients,100%). Infiltrates were seen in 5 (16%) patients.

Table No. 9: Tabular representation of Chest X-Ray findings.

CHEST X-RAY FINDINGS				
	Males	Female	Total	Percentage
BILATERAL BASAL RETICULAR PATTERN	1	29	30	100%
REDUCED LUNG VOLUME	1	29	30	100%

INFILTRATES	**0**	**5**	**5**	**16%**

Most common High resolution computed tomography pattern was Non-Specific interstitial pneumonia (in 22 patients, 73.3%), followed by Usual interstitial pneumonia (in 6 patients, 20%) and Organizing pneumonia (in 2 patients, 6.7%).

Table No. 10: Tabular representation of HRCT findings

HIGH RESOLUTION CT PATTERNS				
	Males	**Female**	**Total**	**Percentage**
NON SPECIFIC INTERSTITIAL PNEUMONIA	**1**	**21**	**22**	**73.3%**
USUAL INTERSTITIAL PNEUMONIA	**-**	**6**	**6**	**20%**
ORGANIZING PNEUMONIA	**-**	**2**	**2**	**6.7%**

Most common findings in HRCT include irregular linear opacities (in 23 patients, 76.6%) and ground glass opacities (in 18 patients, 60%) followed by Reticular pattern (in 12 patients,40%), Honey comb appearance (in 7 patients, 23.3%), Traction Bronchiectasis (in 7 patients, 23.3%) and Consolidation (in 5 patients,16.6%).

Table No. 11: Tabular representation of High resolution CT findings.

HRCT FINDINGS				
	Males	**Female**	**Total**	**Percentage**
IRREGULAR LINEAR OPACITIES	**1**	**22**	**23**	**76.6%**
GROUND GLASS OPACITIES	**-**	**18**	**18**	**60%**
RETICULAR PATTERN	**-**	**12**	**12**	**40%**
HONEY COMB APPEARANCE	**1**	**6**	**7**	**23.3%**
TRACTION BRONCHIECTASIS	**1**	**6**	**7**	**23.3%**
CONSOLIDATION	**-**	**5**	**5**	**16.6%**

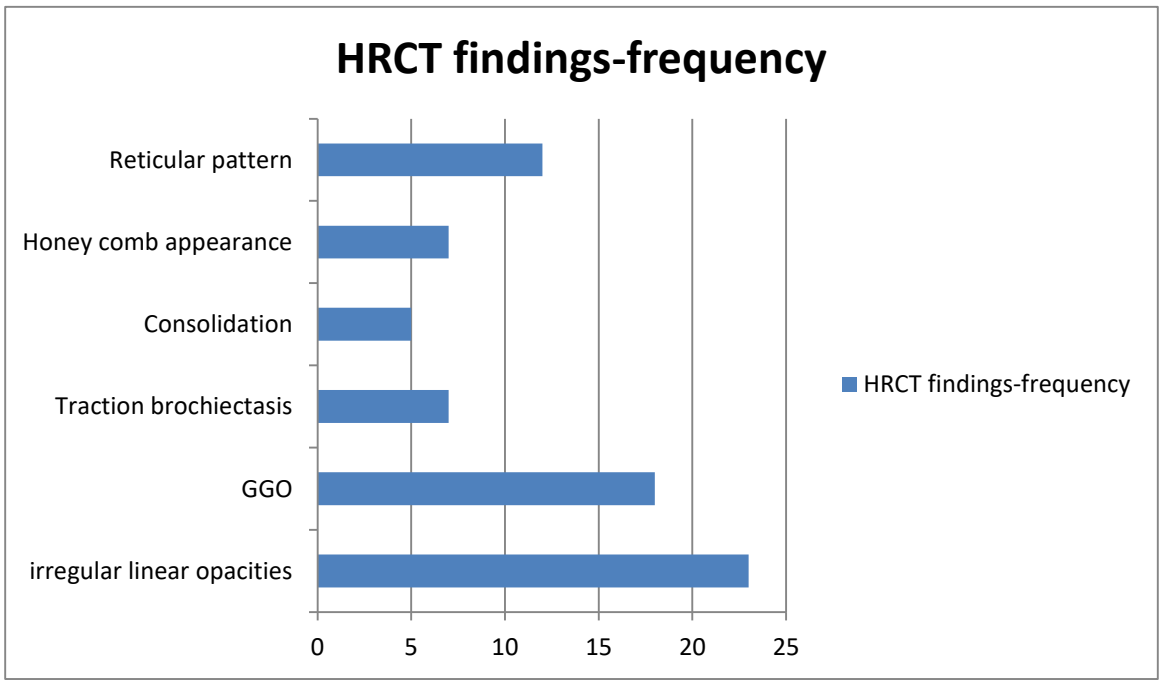

Figure 3.Graphical representation of HRCT findings

Most common pattern in the present study was Restrictive pattern (in 25 patients, 83.4%), followed by mixed pattern (in 4 patients, 13.3%). Spirometry was not done in one patient (3.3%) due to severe disability.

Table No. 12: Tabular representation of Spirometry findings

SPIROMETRY				
	Males	**Females**	**Total**	**Percentage**
RESTRICTIVE	**1**	**24**	**25**	**83.4%**
MIXED	**-**	**4**	**4**	**13.3%**
NOT DONE	**-**	**1**	**1**	**3.3%**

Of the 25 patients found to have restrictive pattern in spirometry, 4 patients (16%) were having Very-severe restriction. Severe restriction is found in 4 patients (16%). Moderately-severe restriction is seen in 10 patients (40%). Moderate restriction is seen in 3 patients (12%) and Mild restriction was found in 4 patients (16%). For 25 patients with restrictive pattern, percentage predicted value was 53.4 ± 13.9.

Table No. 13: Tabular representation of severity of Restriction in spirometry.

SEVERITY OF RESTRICTION IN SPIROMETRY (ATS/ERS)				
	Males	**Female**	**Total (n=25)**	
MILD (FEV1 > 70%)	**-**	**4**	**4**	
MODERATE (FEV1 60 - 69%)	**-**	**3**	**3**	**Percentage Predicted**
MODERATELY SEVERE (FEV1 50 - 59%)	**-**	**10**	**10**	**53.4 ± 13.9**
SEVERE (FEV1 35 - 49%)	**1**	**3**	**4**	
VERY SEVERE (FEV1 < 35%)	**-**	**4**	**4**	

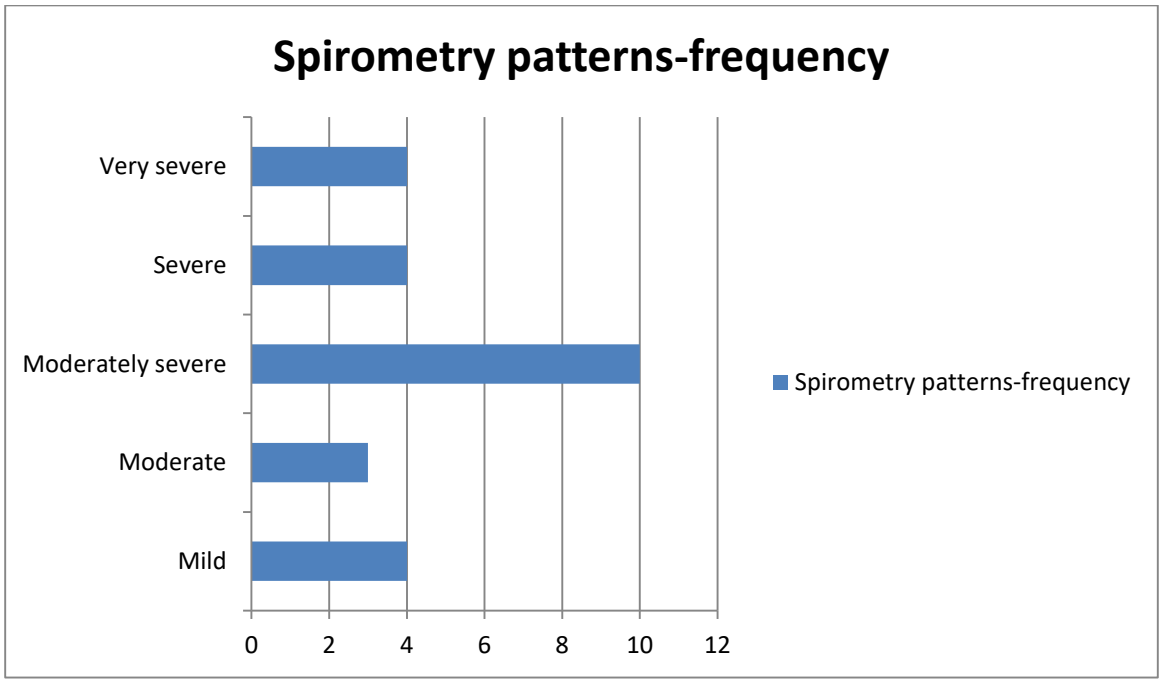

Figure 4.Graphical representation of spirometry findings

23 patients (76.7%) were found to have Pulmonary Artery hypertension in 2D-Echo. Other findings include Raised RVSP (in 23 patients, 76.7%) and Tricuspid Regurgitation (in 11 patients,36.6%).

Table No. 14: Tabular representation of 2D-Echo findings

2D – ECHO FINDINGS				
	Males	**Females**	**Total**	**Percentage**
PULMONARY ARTERY HYPERTENSION	**1**	**22**	**23**	**76.7%**
RAISED RVSP	**1**	**22**	**23**	**76.7%**

TRICUSPID REGURGITATION	**1**	**10**	**11**	**36.6%**

Of the 30 patients, 23 were found to have Pulmonary artery hypertension, eight patients (35%) were having severe PAH. Moderate and Mild PAH were found in 12 patients (52%) and 3 patients (35%) respectively. Mean of RSVP is 55.5 ± 8.4.

Table No. 15: Tabular representation of severity of PAH in 2D-Echo.

SEVERITY OF PAH IN 2D - ECHO				
	Males	**Female**	**Total (n=23)**	**Percentage**
MILD (RVSP 35 – 45 mmHg)	**-**	**3**	**3**	**13%**
MODERATE (RVSP 46 – 60 mmHg)	**-**	**12**	**12**	**52%**
SEVERE (RVSP >60 mmHg)	**1**	**7**	**8**	**35%**

Antinuclear antibody is positive in all cases. Most commonly found autoantibodies were Anti- Scl70 Ab (in 11 patients, 36.6%), Anti-Centromere Ab (in 11 patients, 36.6%), followed by Anti-Ro-Anti-La Ab (in 1 patient, 3.3%) and Anti-Smith Ab (in 1 patient, 3.3%). Other antibodies include Anti-RNP Ab (in 9 patients, 30%), Rheumatic Factor (in 7 patients, 23.3%), Anti-CCP Ab (in 7 patients, 23.3%), Anti-Jo Ab (in 1 patient, 3.3%) and Anti- RNA Synthetase Ab (in 1 patient, 3.3%).

Table No. 16: Tabular representation of Serological Profile.

SEROLOGICAL PROFILE				
	Males	**Female**	**Total**	**Percentage**
ANTI-Scl70	**-**	**11**	**11**	**36.6%**
ANTI-CENTROMERE Ab	**-**	**11**	**11**	**36.6%**
ANTI-Ro Ab & ANTI-La Ab	**-**	**-**	**1**	**3.3%**
ANTI-SMITH Ab	**1**	**-**	**1**	**3.3%**
ANTI-RNP Ab	**-**	**9**	**9**	**30%**
RHEUMATIC FACTOR	**-**	**7**	**7**	**23.3%**
ANTI-CCP Ab	**-**	**7**	**7**	**23.3%**
ANTI-NUCLEAR Ab	**1**	**29**	**30**	**100%**
ANTI-Jo Ab	**-**	**1**	**1**	**3.3%**
ANTI-RNA-SYNTHASE Ab	**-**	**1**	**1**	**3.3%**

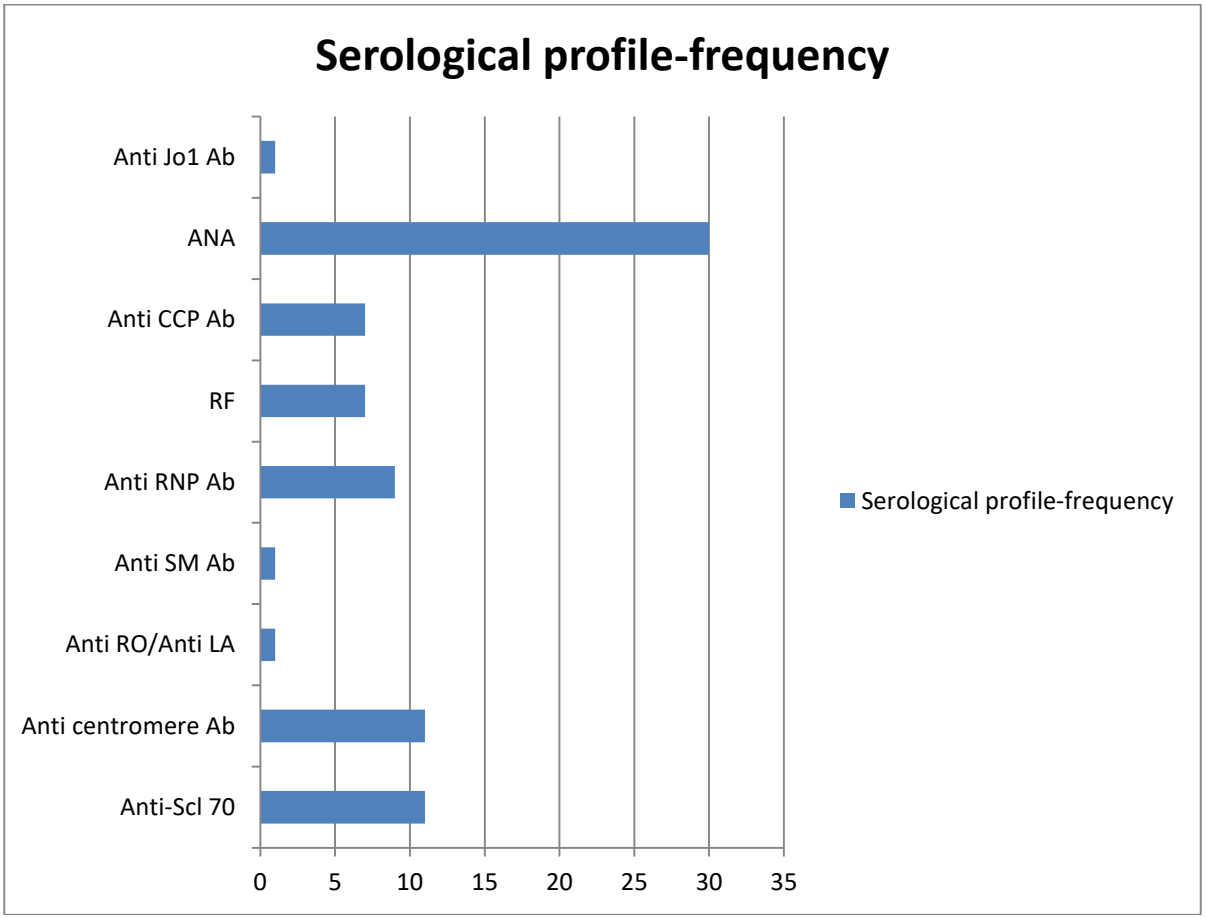

Figure 5.Graphical representation of serology profile

Scleroderma (in 11 patients, 36.7%) was the most commonly associated connective tissue disorder followed by Mixed connective tissue disorder (in 9 patients,30%) and Rheumatoid Arthritis (in 7 patients,23.4%). Sjogren's syndrome, Systemic Lupus Erythematosus and polymyositis were found in one patient (3.3%) each.

Table No. 17: Tabular representation of Associated CTDs.

ASSOCIATED CONNECTIVE TISSUE DISORDERS				
	Males	Females	Total	Percentage
SCLERODERMA	-	11	11	36.7%
MIXED CTD	-	9	9	30%
RHEUMATOID ARTHRITIS	-	7	7	23.4%
SJOGREN'S	-	1	1	3.3%
SYSTEMIC LUPUS ERYTHEMATOSUS	1	-	1	3.3%
POLYMYOSITIS	-	1	1	3.3%

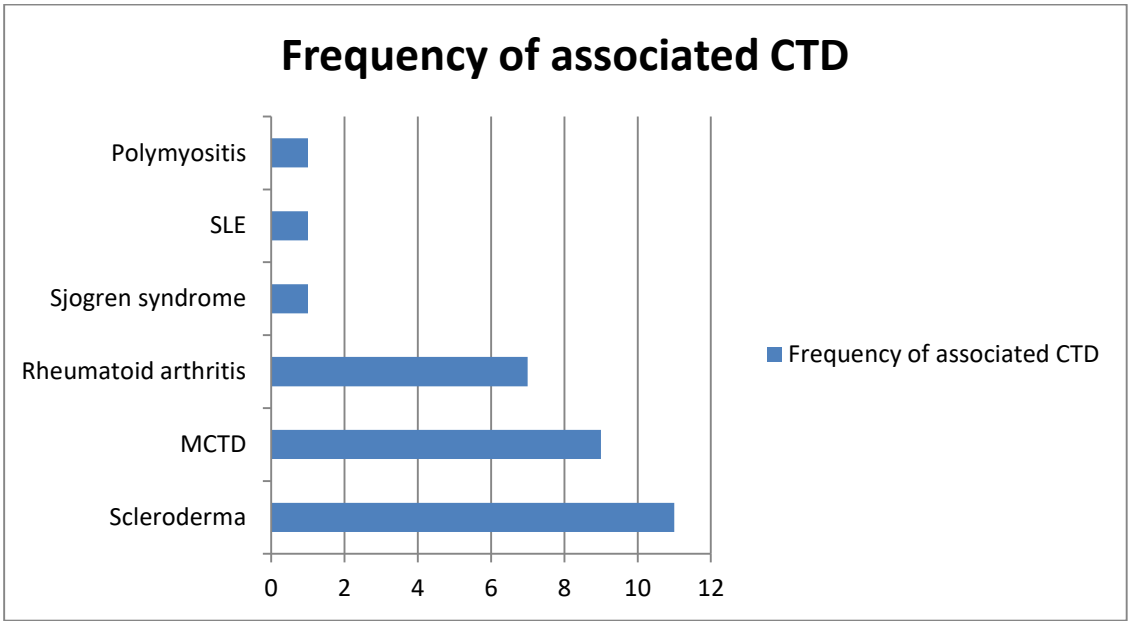

Figure 6.Graphical representation of associated CT

III. CONCLUSION

Systemic sclerosis was most commonly associated CTD-ILD followed by mixed connective tissue disease and rheumatoid arthritis.Most commonly found antibodies were ANA, Anti-Scl-70 Ab, Anti-Centromere followed by Anti-CCP and Anti-RNP.Cough and Shortness of breath were the most common clinical presentations. Other extra pulmonary symptoms like arthralgia, morning stiffness and GERD.Restrictive pattern was the most common pattern in Spirometry.Most commonly seen HRCT pattern was Non-specific Interstitial pneumonia. PAH was the most common 2D-Echo finding.All patients with CTDs should be systematically evaluated and monitored for pulmonary involvement so that early recognition and introduction of the therapy will help in preventing the morbidity and mortality.Many pulmonary manifestations are common in patients with CTDs, ILD being the most common pulmonary involvement. Some manifestations may remain asymptomatic or can progress gradually resulting in morbidity and mortality.Most of the cases of CTD-ILD were found based on HRCT.

LIMITATIONS OF THE STUDY

1. Sample size was very small.
2. Duration of the study was limited.
3. Follow up of each case to observe prognosis in each type of CTD.
4. Duration of CTD prior to pulmonary manifestation and treatment history for ILD were not taken in the present study

Future Directions

Large multi-centre studies conducted in India regarding profile of CTD-ILD are needed to derive at significant conclusion.

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