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# THE PREVALENCE OF INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS PATIENTS



ABSTRACT

**OBJECTIVE:** To report the prevalence of interstitial lung disease in Systemic Sclerosis patients at the Royal Hospital and compare our data with the literature.

METHODS: All adult Omani patients with Systemic Sclerosis (SSc) who are under regular follow-up at the Royal Hospital were retrospectively enrolled from January 2006 to January 2014.

**RESULTS:** A total of 49 cases of Systemic Sclerosis (SSc) patients were included. The mean age was  $44.06 \pm 11.9$  years. There was a predominance of females (48 cases; 98%). Interstitial lung disease present in 30 cases (61%). The most frequent symptoms were dyspnea 47%, cough 33%, and others (e.g. atypical chest pain) 20%. There was no association with smoking, non-smoker (47 cases, 95.5%) versus ex. smoker (2 cases, 4%). The most high resolution computed tomography (HRCT) finding was traction bronchiectasis (21 cases, 42.9%) followed by honey comb appearance (19 cases, 38.8%). Pulmonary Function Test (PFT) was done in 33 cases. The mean total lung capacity (TLC) was 81.06  $\pm$  26.2. The mean diffusion lung capacity (DLCO) was  $61.8\pm$  28.3. Pulmonary hypertension was found in 10 cases only (20.4%) based on echocardiography.

**CONCLUSIONS:** ILD was present in 30 cases out of 49 cases of SSc (61.2%) with female predominance. The most frequently observed HRCT change was traction bronchiectasis. Similarities and differences were found with respect to the previous reports from other countries.

# **KEYWORDS**

Connective Tissue Disease, Systemic Sclerosis, Scleroderma, Interstitial Lung Disease.

# **INTRODUCTION:**

Interstitial lung disease (ILD) is a diverse group of disorders that diffusely affects the lung parenchyma (1). It has variable etiologies, clinical presentations, radiographic patterns, and histological appearances (1). Although, there is significant improvement in understanding the various causes of ILD, its diagnosis can be very challenging and requires significant expertise in chest medicine, rheumatology, radiology, and histopathology (1). There are relatively a small number of epidemiological studies on ILD in SSc patients , but the existing studies show that there are wide variations in the incidence and prevalence of the various ILD between countries(1). Based on the updated American Thoracic Society/ European Respiratory Society, diffuse parenchymal lung disease classified as follow; secondary to connective tissue diseases e.g.: systemic lupus erythematous, rheumatoid arthritis, systemic sclerosis, drugs, occupation, Idiopathic, granulomatous, and miscellaneous(2). Microvascular change is an early manifestation of systemic sclerosis followed by intimal proliferation and fibrosis of arterioles resulting in reduced blood flow and tissue ischemia (3). Possible pathogenic mechanisms have been delineated but the causes still remains unknown (4). SSc is a clinically heterogeneous, multi-system autoimmune disease (5). The hallmark clinical feature consists of thickening and tightening of the skin and internal organs such as the lungs, gastrointestinal tract and kidneys (6). Pulmonary involvement is common in patients with SSc and most often include fibrosis and pulmonary vascular disease leading to pulmonary arterial hypertension (5). Pulmonary complications are the leading cause of disease related morbidity and mortality in patients with SSc(5). It has been difficult to define the epidemiology of ILD in SSc with any degree of accuracy, this reflect the fact that SSc is rare disease (estimated prevalence 30-500/million) (14). Previous studies of ILD suggest that therapeutic and prognosis responses are influenced by the presence of underlying connective tissue disorders (8).

# METHODS

**Study population**: This is a retrospective study. All adult Omani patients with SSc who are on regular follow up at Royal Hospital (a tertiary care institution, Muscat, Oman) from January 2006 to January 2014 were included in this study. SSc was diagnosed based on 2013 American College of Rheumatology (ACR)/European League Against Rheumatism Collaborative Initiative (EULAR) criteria for the classification of systemic sclerosis, as shown in table 1.

**Ethics:** This study was approved by the Research Committee at the Royal Hospital (Muscat, Oman), reference #40/2014.

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**Statistical analysis:** The sample size calculated according to the number of patients and confidence interval so sample size required is calculated by using the open EPI data software. The number of patients with SSc who are in follow up regularly is 60 before exclusion of few patients, due to mislabel them as SSc (confidence interval 5%), so the sample size is calculated about 53. Descriptive statistics (mean, standard deviation, percentage) used to describe the quantitative and categorical study variables.

# Table 1: 2013 ACR / EULAR Criteria for the Classification of Systemic Sclerosis

Item	Sub- items(s)	Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints. (sufficient criterion)	-	9
Skin thickening of the	Puffy fingers	2
finger score).	Sclerodactyl of the fingers (distal to the metacarpo phalangeal joints but proximal to proximal interphlangeal joints).	4
Fingertip lesions (only	Digital tip ulcers	2
count the finger score).		2
	Fingertips pitting scar	3
Teleangictasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial	Pulmonary arterial	2
hypertension and /or	hypertension	2
interstitial lung disease	Interstitial lung disease	
Raynaude's phenomenon	-	3
SSc related autoantibodies	anticentromere,	3
(anticentromere, anti	anti topoisomerase I	
topoisomerase I, anti RNA polymerase III)	anti RNA polymerase III	

### RESULTS

The study population included 49 patients. The mean age of the participants was  $44.06 \pm 11.9$  years. There was a predominance of **Accepted : 17<sup>th</sup> October,2019 Publication : 01<sup>st</sup> November, 2019** 

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females (48 cases; 98%). ILD present in 30 cases (61%) as shown in pie chart 1. The most frequent symptoms were: dyspnea 47% and cough 33% as shown in pie chart 2. There was no association with the smoking (47 cases, 95.5% non-smoker versus 2 cases, 4% ex. smoker). There were no significant co morbid conditions neither pulmonary nor cardiac (e.g. asthma, COPD, bronchiectasis, coronary artery disease). The most HRCT findings was traction bronchiectasis (21 cases, 42.9%) followed by honey comb appearance (19 cases, 38.8%), ground glass (14 cases, 28.6%), reticular changes (9 cases, 18.4%), and nodular changes (6 cases, 12.2%) as shown in pie chart 3.



28%

# Pie chart #2 symptoms Pie chart #3 HRCT finding of ILD distribution in Ssc.

The most common distribution in HRCT was bilateral, and sub pleural (51%, 42.9% consequently). PFT was done in 33 cases. The mean total lung capacity (TLC) was  $81.61 \pm 26.25$ . The mean diffusion lung capacity (DLCO) was  $61.8 \pm 28.3$  as shown in table 2. Pulmonary hypertension was found in 10 cases only (20.4%). The commonest antibody present was antinuclear antibody ANA (37 cases, 75%), followed by anti-scleroderma 70 antibody (10 cases, 20.4%). About 46 cases (93.3%) were on steroid, 13 cases (26%) on biologic agent e.g infliximab, and 3 cases (6.1%) on Perfenidone.

# Table 2

	Total Lung Capacity (TLC)	DLCO
Mean	81.6190	61.8077
Std. Deviation	26.25162	28.36902

# DISCUSSION

This study demonstrates that, among patients diagnosed with SSc, enrolled at a single center in Sultanate of Oman, ILD was the most frequent pulmonary disease entities.

The number of cases documented over the period of our study may not be a true reflection of the extent of the disorders in Oman because some of the patients could have been treated in other hospitals.

Epidemiological studies are important tools for measuring the magnitude of health problems, identifying the etiology of a disorder, and facilitating the formation of health care plans for disease prevention and management. Previous study populations for ILD in Gulf countries and international have provided useful information on the prevalence and incidence of the various types. However, these have been limited by differences in study design, diagnostic methods and criteria.

This study shows that, ILD is a common pulmonary complication among SSc patients. The mean age of the patients was  $44.06 \pm 11.9$ years with a predominance of females. This finding is similar to the finding in study was done in Kuwait which showed ILD occurs predominantly in middle-aged and elderly patients (9). Another study done in Saudi Arabia showed the same, the mean age of the participants was  $55.4 \pm 14.9$  years. There was a slight predominance of females (1). In another French study, conducted in France, multi-ethnic country, involved different ethnicity European and non-European (Morocco, Algeria, Tunisia, Asia, sub Saharan Africa, French Caribbean island, American pacific) patients showed the mean age of the disease was 40-59 in different ethnicity(10). This finding of age involvement supports our finding.

Furthermore, smoking has been implicated as one of the environmental risk factors triggering ILD in SSc patients. However, our study showed that there was no association with smoking. It appears that cigarette smoking was not a risk factor. Nevertheless, it remains possible that cigarette smoking may just be one of the risk factors involved in the pathogenesis of ILD in SSc patients. Equally important is the fact that the percentage of females to males was 98%. This finding in our study correlate well with the finding in the study was done in Kuwait which showed there is no significant association between smoking and development of interstitial lung disease (9). Due to the predominance of women and the limitation of the sample size, it may not be enough to conclude that smoking is not a risk factor for the disease.

This study shows the commonest symptoms of ILD was dyspnea on exertion, which may be accompanied by nonproductive cough. This finding is similar to the study which was done in the University of Pittsburgh which showed that the most common cardiopulmonary symptom was exertional dyspnea (11).

HRCT has become the gold standard for diagnosis of SSc associated ILD especially in early stages of the disease (6). It is a much more sensitive diagnostic test than the traditional chest radiograph, especially for detection of mild or early disease (6). This study shows the most common radiologic pattern of lung disease in systemic sclerosis patients is traction bronchiectasis followed by honey comb and it is predominantly bilateral in distribution. This pattern is different from other international study which shows interstitial lung disease characterized by prominent ground-glass opacities and fine interstitial reticular markings with lower lung predominance (6). As the disease advances, ground-glass opacifications get replaced with coarser interstitial reticulations, traction bronchiectasis and bronchiectasis (6). This difference may be attributed to the late detection of pulmonary complications in SSc patients. In addition, in our setting, HRCT is not done as a routine work up for the pt with SSc unless the patient has pulmonary complaint.

The mean (TLC) was  $81.61 \pm 26.25$ . The mean (DLCO) was  $61.8 \pm 28.3$  this finding of PFT in SSc associated ILD patients is similar to that done in Kuwait (9).

Pulmonary hypertension was present in 10 cases (20.4%). It was based on Echocardiography. Echocardiography is considered the technique of choice to screen for pulmonary hypertension (12). However, estimation of systolic pulmonary artery pressure may be inaccurate, especially in patients with interstitial lung disease. One study was done at Royal Free Hospital, London confirmed that pulmonary hypertension is a common complication of both limited and diffuse systemic sclerosis patients (15).

The anti-nuclear antibody was the most frequently positive autoantibody 77%, and this finding also similar to another regional study (1).

The strength of the study that it is the first study done in Sultanate of Oman to detect the prevalence of ILD in SSc patients. In addition, regionally there is very limited number of studies done for the same purpose.

This study does have some limitations. First, it was based in a single academic center that devotes significant time and resources to the study of ILD and, thus, our data may not represent the situation in other hospitals. Second, the limitation of the sample size is another challenge and may contribute to some differences in the finding compare to others. A larger sample size may give better and accurate result. Third, the majority of the enrolled patients were diagnosed with ILD, based on HRCT scan while in other studies done internationally and regionally some invasive methods were used (e.g trans bronchial biopsies and bronchoalveolar lavages) to detect ILD in earlier stages. And this, may contribute to some differences in the result.

#### **CONCLUSION:**

ILD commonly develops in patients with SSc. HRCT has become the gold standard for evaluation and detection of lung involvement in SSc

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patients. Comparison of our findings with reports from other countries revealed both similarities and di erences. We believe that a future prospective global multicenter epidemiological study is needed to establish the true incidence of various SSc associated ILD among different countries. This will improve our understanding of the natural history of the disease and will aid in identifying appropriate targets for therapeutic interventions.

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#### **Conflict of interest:**

The authors declare that there are no conflicts of interest.

#### Author's contribution:

Dr. Julyan Al Fori was the primary researcher who collected, nalized, interpreted the data, prepared the first draft of the manuscript and reviewed the literature. Dr. Nasser Al Busaidi supervised the study design, data interpretation and revised the manuscript. All authors reviewed and approved the final manuscript.

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