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Original Article

Internal Medicine Section

Cardiopulmonary Involvement in Patients with Systemic Sclerosis: A Cross-sectional Study

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ABSTRACT

Introduction: One of the most challenging aspects of systemic sclerosis is the potential involvement of the cardiopulmonary system, which can lead to significant morbidity and mortality if not detected and managed promptly.

Aim: To assess the clinical characteristics and prevalence of specific cardiopulmonary involvement and to investigate its association with disease duration in patients with systemic sclerosis from South India.

Materials and Methods: This cross-sectional, observational study was conducted at the Department of General Medicine, Government Medical College, Thrissur, India, between January 1, 2020, and December 31, 2020. Forty patients with systemic sclerosis were included according to the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology classification criteria. Skin thickening was evaluated using the modified Rodnan Skin Score (mRSS). Investigations such as chest X-ray, echocardiogram, and antibody profiling were conducted to evaluate cardiopulmonary involvement. The data were analysed using Statistical Package for Social Sciences (SPSS) version 23.0, and the Chi-square test was used to compare qualitative variables between groups.

Results: Sixteen patients (40%) had an mRSS score between 11 and 20, followed by 14 patients (35%) with mRSS scores between 21 and 30. The prevalence of Interstitial Lung Disease (ILD) was 50%. The echocardiogram findings showed mitral regurgitation and moderate Pulmonary Arterial Hypertension (PAH) in 30% (n=12) and 25% (n=10) of patients, respectively. High-Resolution Computed Tomography (HRCT) and pulmonary function tests were normal in 10 patients (25%). The duration of the disease was three to eight years in 14 patients and eight to 12 years in 12 patients. Both ILD and PAH were significantly associated with the duration of the disease ($p<0.05$). Anti-scleroderma-70 and anti-centromere were the most common antibodies present in patients with ILD and PAH, respectively.

Conclusion: The study indicated a high prevalence of PAH and ILD in patients with systemic sclerosis. Moreover, both ILD and PAH were significantly associated with the duration of the underlying disease, with longer disease duration being associated with a higher likelihood of these conditions.

Keywords: Left ventricular hypertrophy, Lung disease, Pulmonary arterial hypertension, Scleroderma

INTRODUCTION

Systemic sclerosis is a connective tissue disease clinically represented by hidebound skin and organ compromise [1,2]. It is characterised by vascular dysfunction, skin and visceral fibrosis, and is divided into two groups: limited and diffuse cutaneous disease [3-5]. The limited form includes skin thickening distal to the elbows and knees, with less severe internal organ involvement. The diffuse form affects the skin proximal to the elbows and knees as well as the distal areas, where more severe organ damage is present [4].

Manifestations of systemic sclerosis can occur in various tissues and organs, with cardiac involvement being one of the leading causes of mortality [3]. Cardiac manifestations may result in pericardial effusion, arrhythmias, conduction system defects, valvular regurgitation, myocardial ischaemia, myocardial hypertrophy, and heart failure [6,7]. Cardiac involvement in systemic sclerosis can include direct (primary) myocardial effects such as myositis, cardiac failure, cardiac fibrosis, coronary artery disease, and pericardial disease, or indirect (secondary) effects of other organ involvement such as PAH, ILD, or kidney disease [8,9].

Pulmonary Arterial Hypertension (PAH) is defined as a mean pulmonary artery pressure ≥25 mmHg, as determined by Right Heart Catheterisation (RHC), and it affects about 8-12% of patients with systemic sclerosis [10,11]. Systemic sclerosis patients with PAH are associated with a >3-fold increased risk of death compared to those without PAH [11]. Symptoms of indolent, progressive shortness of breath, pedal oedema, ascites, and congestive hepatomegaly are usually presented by patients with pulmonary hypertension and subsequent right heart failure [8]. Symptoms of severe pulmonary hypertension may include syncope and sudden cardiac death, most likely caused by arrhythmias or acute right ventricular failure [8].

On the other hand, ILD in patients with systemic sclerosis is a relatively limited and slowly progressive condition in limited cutaneous form, whereas it has a rapidly progressive nature in diffuse systemic sclerosis [10]. Although the primary pathway in the pathogenesis of ILD associated with systemic sclerosis has not been definitively identified, the progression of lung disease can be retarded by the early identification and assessment of ILD using High-Resolution Computed Tomography (HRCT) [12].

The early cardiac manifestations of systemic sclerosis are often non-specific, and patients may therefore remain undiagnosed, potentially enabling the silent progression of the disease [6]. Detection of ILD and PAH at an early pre-symptomatic stage and individually tailored therapy can help manage the disease [4]. While several studies are available demonstrating cardiopulmonary involvement in scleroderma patients [13-16], only a few have discussed its association with disease duration [17,18].

Therefore, the present study aimed to assess the clinical characteristics and prevalence of specific cardiopulmonary involvement and to investigate their association with disease duration in patients with systemic sclerosis from South India.

MATERIALS AND METHODS

This cross-sectional, observational study was conducted in scleroderma patients at the Department of General Medicine, Government Medical College, Thrissur, India, between January 1, 2020, and December 31, 2020. The study was based on the revised

systemic sclerosis classification criteria by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) [19]. The study was approved by the Institutional Ethics Committee, and the study procedures were in accordance with the principles of the Declaration of Helsinki {Approval No. B6-155/2019/MCTCR (14)}. Written informed consent was obtained from all study patients before enrolment.

Inclusion criteria: The study included patients with systemic sclerosis, of either gender, attending the Medicine and Rheumatology Clinic.

Exclusion criteria: Those patients with features of mixed and undifferentiated connective tissue disorder, overlap syndrome, a previous history of pulmonary tuberculosis, occupational lung disease, idiopathic pulmonary fibrosis, and those unwilling to provide consent were excluded from the study.

Sample size calculation: Based on observations from the previous year, where approximately 40 scleroderma patients attended the Rheumatology clinic and Medicine department, this study aimed to investigate scleroderma patients in greater detail. The population size was arbitrarily fixed at 40 based on clinical observation.

Procedure

All patients satisfying the inclusion criteria attending the OPD and IP of the Rheumatology clinic and Medicine department during the defined time period of the study were included.

Skin thickening was evaluated using the mRSS [20]. The skin thickening was assessed by palpation of the skin in 17 areas of the body (fingers, hands, forearms, upper arms, face, anterior chest, abdomen, thigh, leg, and feet). The score is given as follows:

- 0- no thickening,
- 1- mild thickening,
- 2- moderate thickening,
- 3- severe thickening.

Trained healthcare professionals performed clinical examinations, echocardiography, chest X-rays, and High-Resolution Computed Tomography (HRCT) scans. Pulmonary Function Tests (PFTs) were conducted by certified respiratory therapists. Investigations such as chest X-ray, Echocardiogram (ECHO) and antibody profiles were also collected and analysed.

STATISTICAL ANALYSIS

The data were analysed using the SPSS software version 23.0. Qualitative data were presented as numbers and percentages. A comparison of qualitative variables between the groups was performed using the Chi-square test. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 40 patients were enrolled in the study, all of whom were female. The mean age of the study population was 45.1 (SD 8.2) years. [Table/Fig-1] depicts the clinical and imaging findings of the patients.

Parameters	n (%) (Total N=40)
mRSS	
0 to 10	10 (25.0)
11 to 20	16 (40.0)
21 to 30	14 (35.0)
Echo cardiogram findings	
Normal	21 (52.5)
Concentric LVH	2 (5.0)
MR	12 (30.0)
Moderate PAH	10 (25.0)
Mild PAH	4 (10.0)
Chest X-ray findings	
Normal	17 (42.5)
Fibrosis	5 (12.5)
Bronchiectatic shadows	10 (25.0)
Reticular opacity	16 (40.0)
HRCT findings	
Normal	10 (25.0)
Fibrosis	9 (22.5)
Traction bronchiectasis	9 (22.5)
Reticular opacities	5 (12.5)
Ground glass	5 (12.5)
Honeycombing	10 (25.0)
Septal thickening	5 (12.5)
PFT findings	
Normal	10 (25.0)
Mild restriction	9 (22.5)
Moderate restriction	14 (35.0)
Moderately severe restriction	2 (5.0)
Severe restriction	5 (12.5)
Antibodies	
Anti-centromere antibody	23 (57.5)
Anti-scl70	17 (42.5)
Anti-Ro52	2 (5.0)

[Table/Fig-1]: Clinical and imaging findings {Number of patients (N=40)}.
Data presented as n (%); HRCT: High-resolution computed tomography; LVH: Left ventricular hypertrophy; MR: Mitral regurgitation; mRSS: modified Rodnan skin score; PAH: Pulmonary arterial hypertension; PFT: Pulmonary function tests; scl70: scleroderma-70

The mRSS scores were 0-10 in 25% of patients, 11-20 in 40% of patients, and 21-30 in 35% of patients. Echocardiography (ECHO) findings were normal in half of the study population (52.5%), while mitral regurgitation and moderate PAH were observed in 30% (n=12) and 25% (n=10) of patients, respectively. Chest X-ray findings were normal in 17 (42.5%) patients, while reticular opacity, bronchiectatic shadows, and fibrosis were found in 16 (40%), 10 (25%), and 5 (12.5%) patients, respectively. HRCT and PFT findings were normal in 10 patients (25%) each. Anti-centromere antibody was most commonly found in 23 (57.5%) patients [Table/Fig-1].

The association of disease duration with ILD and PAH is given in [Table/Fig-2]. The prevalence of ILD and PAH was 50% (n=20) and 35% (n=14), respectively. The majority of patients (n=14; 35%) had a disease duration of >2 to ≤8 years.

Parameters	ILD present	ILD absent	p-value	PAH present	PAH absent	p-value
Duration of disease						
≤2 years (n=10)	0	10 (25)	**<0.001**	1 (2.5)	9 (22.5)	**0.02**
>2 to ≤8 years (n=14)	7 (17.5)	7 (17.5)		2 (5)	12 (30)	
>8 to ≤12 years (n=12)	10 (25)	2 (5)		8 (20)	4 (10)	
>12 years (n=4)	3 (7.5)	1 (2.5)		3 (7.5)	1 (2.5)	

[Table/Fig-2]: Association of duration of disease with ILD and PAH.
Data presented as n (%); ILD: Interstitial lung disease; PAH: Pulmonary arterial hypertension; Statistical test used: Chi-square test

The prevalence of ILD and PAH tends to increase with the duration of the disease. Both ILD and PAH were significantly associated with the disease duration ($p<0.05$) [Table/Fig-2].

However, there was no association between mRSS and the disease duration, as well as the presence of ILD and PAH ($p>0.05$) [Table/Fig-3]. Anti-scleroderma-70 antibody was the most common antibody present in patients with ILD, while anti-centromere antibody was more prevalent in patients with PAH [Table/Fig-4].

Parameters	mRSS (0 to 10)	mRSS (11 to 20)	mRSS (21 to 30)	p-value
Duration of disease				
≤2 years	2 (5.0)	4 (10.0)	4 (10.0)	0.907
>2 to ≤8 years	5 (12.5)	4 (10.0)	5 (12.5)	
>8 to ≤12 years	2 (5.0)	6 (15.0)	4 (10.0)	
>12 years	1 (2.5)	2 (5.0)	1 (2.5)	
ILD				
Present	6 (15.0)	6 (15.0)	8 (20.0)	0.430
Absent	4 (10.0)	10 (25.0)	6 (15.0)	
PAH				
Present	4 (10.0)	7 (17.5)	3 (7.5)	
Absent	6 (15.0)	9 (22.5)	11 (27.5)	

[Table/Fig-3]: Association of mRSS with duration of disease, ILD and PAH.
Data presented as n (%); ILD; interstitial lung disease; mRSS: modified Rodnan skin score; PAH: Pulmonary arterial hypertension; Statistical test used: Chi-square test

Antibodies	ILD present	ILD absent	p-value	PAH present	PAH absent	p-value
Anti-centromere Anti-body	3 (7.5)	20 (50.0)	<0.001	10 (25.0)	13 (32.5)	0.623
Anti-scl70	17 (42.5)	0		5 (12.5)	12 (30.0)	
Anti-Ro52	2 (5.0)	0		1 (2.5)	1 (2.5)	

[Table/Fig-4]: Association of presence of antibodies with ILD and PAH.
Data presented as n (%); ILD: Interstitial lung disease; PAH: Pulmonary arterial hypertension; scl70: scleroderma-70; Statistical test used: Chi-square test

DISCUSSION

ILD is a common manifestation in systemic sclerosis, and research indicates its occurrence in a substantial proportion of patients [21-23]. PAH is another critical complication, particularly in advanced stages of systemic sclerosis [24-26]. Understanding the prevalence of these complications is crucial for timely diagnosis and management. The present study aimed to determine predictors of cardiopulmonary involvement in systemic sclerosis. In this study, chest X-ray findings were normal in 17 (42.5%) patients, while reticular opacity, bronchiectatic shadows, and fibrosis were found in 16 (40%), 10 (25%), and 5 (12.5%) patients, respectively. These findings align with previous studies. Arakkal G et al., conducted a study on cardiopulmonary involvement in systemic sclerosis, where abnormal chest X-ray findings were observed in 16 (57.1%) patients [4]. Sharma VK et al., also reported abnormal X-rays in 65.3% of the study population [27]. These findings suggest that chest X-ray abnormalities are relatively common among systemic sclerosis patients and can serve as important indicators of cardiopulmonary involvement in this population. Therefore, these results provide valuable insights into the presence of abnormal chest X-ray findings in individuals with systemic sclerosis, enhancing our understanding of the disease's impact on the pulmonary system.

In the present study, PFT was normal in 25% of patients, which is significantly lower compared to the previous study by Sharma VK et al., where 85.8% of patients had abnormal PFT results [27]. Steen VD et al., noted a restrictive disease in 40% (359/890) of patients, with 27% having a moderate restrictive pattern and 13% having a severe restrictive pattern [28]. However, in this study, the prevalence of restrictive pattern was comparatively higher, observed in 75% of patients, with 14% and 5% of patients having moderate and severe restriction, respectively. These findings suggest variability in PFT results among systemic sclerosis patients, highlighting the heterogeneity of the disease. The differences between the current study and previous research conducted by Sharma VK et al., and Steen VD et al., may be attributed to factors such as patient demographics, disease severity, or even the methodology used in PFT assessments [27,28].

Arakkal G et al., reported HRCT features suggestive of ILD in 21 (75%) patients, with ground glass opacities in 14 (66.7%), honeycombing in 12 (57.1%), reticulations in 9 (42.9%), architectural distortion in 10 (47.6%), septal thickening in 10 (47.6%), and tractional bronchiectasis in five (23.8%) patients [4]. In this study, HRCT findings showed septal thickening, ground glass and reticular opacities in five patients each, honeycombing in 10 (25%) patients, and fibrosis and traction bronchiectasis in nine patients. These findings indicate the presence of common radiological characteristics associated with ILD in systemic sclerosis patients. The consistency in HRCT findings underscores the significance of these patterns as potential indicators of ILD in this patient population. It emphasises the importance of early detection and management of pulmonary involvement in systemic sclerosis.

Anti-topoisomerase I auto-antibodies, also known as anti-scleroderma-70 antibodies, are found in approximately 20% of systemic sclerosis patients, most commonly in association with diffuse cutaneous systemic sclerosis. Systemic sclerosis-ILD is most prevalent in patients positive for anti-topoisomerase I auto-antibodies [12]. In this study, approximately 42.5% of patients with anti-scleroderma-70 antibodies exhibited the presence of ILD. On the other hand, anti-centromere antibodies, present in about 20-30% of systemic sclerosis patients, are associated with a low prevalence of systemic sclerosis-ILD. Anti-centromere antibody positivity is associated with limited cutaneous systemic sclerosis and an increased risk of PAH [12]. In the present study, 32.5% of patients with anti-centromere antibodies had PAH. These findings highlight the importance of auto-antibody profiling in systemic sclerosis patients as it can help predict and manage specific clinical manifestations. The detection of anti-scleroderma-70 antibodies may alert clinicians to the potential presence of Systemic Sclerosis (SSc)-ILD, while the presence of anti-centromere antibodies may indicate an increased risk of PAH.

In the present study, the prevalence of ILD and PAH tends to increase with the duration of the disease. Importantly, patients with a longer history of the underlying condition showed a higher likelihood of having ILD and PAH. These findings are consistent with previous research conducted on patients with systemic sclerosis [17,18]. This consistency with prior studies underscores the robustness of the observed association between disease duration and the occurrence of ILD and PAH. It suggests that the relationship between disease duration and these pulmonary complications is a recurring pattern in individuals with systemic sclerosis. Understanding this association is vital for healthcare practitioners as it aids in risk assessment, early detection, and the development of tailored treatment strategies for patients with varying disease durations.

Limitation(s)

Firstly, the sample size of the study may not encompass the full spectrum of systemic sclerosis patients, and there may be variations in disease presentation and severity in a larger and more diverse population. Secondly, the retrospective nature of some data collection, such as disease duration, relies on patient self-reporting and medical records, which may introduce recall bias or incomplete information. Finally, this study primarily focuses on the association between cardiopulmonary involvement and disease duration, and other factors that could influence these outcomes, such as treatment regimens or co-morbidities, were not comprehensively analysed.

CONCLUSION(S)

This study highlights the higher prevalence of ILD and PAH in patients with systemic sclerosis. Furthermore, both ILD and PAH showed significant associations with the duration of the underlying disease, where longer disease duration was associated with a higher likelihood of these conditions. These findings can guide clinicians in devising individualised treatment strategies for systemic sclerosis patients based on their disease duration and specific cardiopulmonary manifestations, ultimately improving patient outcomes and quality of life. However, further research in this area is needed to enhance our understanding and address any remaining questions.

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