Frequency of Disease Subsets and Spectrum of Organ Involvement and Interstitial Lung Disease Patterns in Patients of Systemic Sclerosis in Pakistani Population

Umbreen Arshad[1], Muhammad Ahmed Saeed[1,2,3], Muhammad Rafaqat Hameed[1,2,3], Maryam Aamer[1], Shamas U Din[1] and Hafiz Yasir Qamar[1]

[1]*Department of Rheumatology, Central Park Teaching Hospital, Lahore, Pakistan*
[2]*Department of Rheumatology, National Hospital and Postgraduate Medical Centre, Lahore, Pakistan*
[3]*Department of Rheumatology, Arthritis Care Foundation, Lahore, Pakistan*

ABSTRACT

Objective: To assess the frequency of disease subsets and the spectrum of organ involvement, particularly focusing on interstitial lung disease (ILD) patterns among patients with systemic sclerosis (SSc).

Study Design: Observational study.

Place and Duration of the Study: Institute of Rheumatic Diseases, Central Park Teaching Hospital, and its affiliated Arthritis Care Centre, Lahore, Pakistan, from July 2022 to December 2023.

Methodology: Data were extracted from electronic records and gathered using a questionnaire. Patients were classified into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) subsets based on clinical criteria. Gender, age, duration of disease, clinical features, and ILD patterns were compared between the groups.

Results: The mean age of the 68 (88.3%) female patients was 37.9 ± 11.2 years. Younger patients presented with diffuse scleroderma (36 ± 11.3 years) compared to those with limited scleroderma (40.2 ± 10.7 years). The most common clinical feature was Raynaud's phenomenon (90.9%), followed by digital ulcers (41.6%). ILD was present in 68.8%, with non-specific interstitial pneumonia (NSIP) identified in 31.2%, usual interstitial pneumonia (UIP) in 19.5%, and fibrosing NSIP in 3.9%.

Conclusion: Systemic sclerosis predominantly affects younger females, with a higher diffuse cutaneous subtype. Raynaud's phenomenon is the most common manifestation. ILD is a significant complication, with NSIP being the most common pattern observed.

Key Words: *Systemic sclerosis, Rheumatic diseases, Limited cutaneous systematic sclerosis, Diffuse cutaneous systematic sclerosis*.

How to cite this article: Arshad U, Saeed MA, Hameed MR, Aamer M, Din SU, Qamar HY. Frequency of Disease Subsets and Spectrum of Organ Involvement and Interstitial Lung Disease Patterns in Patients of Systemic Sclerosis in Pakistani Population. *J Coll Physicians Surg Pak* 2025; **35(05)**:646-650.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterised by vasomotor irregularities, fibrosis, and related inflammatory symptoms. This condition impacts both the skin and internal organs, including the digestive tract, lungs, heart, kidneys, and blood vessels.[1] It is a severe illness with potentially life-threatening outcomes. The occurrence and frequency of SSc vary significantly worldwide, with an overall pooled prevalence of 30-120 cases per 100,000[2] and an incidence rate of 1.4 per 100,000 individuals per year.[3]

Correspondence to: Dr. Umbreen Arshad, Department of Rheumatology, Central Park Teaching Hospital, Lahore, Pakistan
E-mail: arshadumbreen@gmail.com
Received: March 20, 2024; Revised: June 15, 2024; Accepted: November 11, 2024
DOI: https://doi.org/10.29271/jcpsp.2025.05.646

Despite its relatively low prevalence, systemic sclerosis has a substantial impact on patients and healthcare systems, carrying the highest mortality rate among all rheumatic diseases.[4]

Systemic sclerosis (SSc) is predominantly more common in females, with a reported female-to-male ratio ranging from 3:1 to 6:1, likely influenced by ethnic and regional factors.[5] The disease is characterised by a diverse range of clinical manifestations,[6] skin sclerosis being a key symptom. This is often assessed using the modified Rodnan skin score (mRSS), an easily identifiable measure of disease activity.[7] Clinically, SSc is categorised based on the degree of skin involvement into two main subtypes: Limited cutaneous SSc (lcSSc), featuring skin thickening distal to elbows and knees, and diffuse cutaneous SSc (dcSSc), characterised by widespread changes in both distal and proximal skin areas.[8]

Cohorts have been established globally to observe the various manifestations of the disease and the different treatments patients receive.[4] Therefore, this study was undertaken to ascertain the distribution of disease subtypes, the spectrum of organ involvement, and the ILD patterns in patients with systemic sclerosis at a tertiary care institution.

METHODOLOGY

This retrospective observational study was carried out at the Institute of Rheumatic Diseases, Central Park Teaching Hospital, and its affiliated Arthritis Care Centre, Lahore, Pakistan, from July 2022 to December 2023. Data from these centres were extracted from electronic records and gathered using a questionnaire. The study included individuals of both genders, aged between 15 and 60 years, who gave consent to the treatment and met the specified criteria for scleroderma. Individuals diagnosed with mixed connective tissue disease, overlapping syndromes, or localised systemic sclerosis (morphea) were excluded. Gender, age, duration of disease, clinical features, and ILD patterns were compared between the groups. ILD patterns were characterised on high-resolution computed tomography (HRCT) of lungs.

The data analysis utilised the statistical software SPSS version 27. Descriptive statistics (mean, standard deviation) were used to summarise quantitative variables, while numbers and percentages were employed for qualitative variables. Categorical variables were compared between groups using the Chi-Square or Fisher's exact test, and a non-parametric Mann-Whitney U test (visualised by histograms) was conducted for continuous variables. Stratification based on gender and types of scleroderma was performed, with statistical significance set at a p-value below 0.05.

Table I: Demographic and clinical characteristics of the scleroderma cohort.

Variables		Mean ±SD	Frequency (n)	Percentage (%)
Age (years)		37.9 ± 11.2		
Age group (years)	15-30		24	31.2
	31-45		33	42.9
	46-60		20	26
Gender	Male		9	11.7
	Female		68	88.3
Age at onset of disease (years)		30.69 ± 11.09		
Duration of disease (years)		7.21 ± 5.57		
Disease subtype	lcSSc		35	45.5
	dcSSc		42	54.5
Manifestations				
Raynaud's phenomenon	Present		70	90.9
Digital pits	Present		28	36.4
Digital ulcers	Present		32	41.6
Gangrene	Present		10	13
Skin	Calcinosis		3	3.9
	Sclerodactyly		71	92.2
	Salt and pepper rash		2	2.6
	Telangiectasia		1	1.3
Musculoskeletal	Arthralgia		37	48.1
	Arthritis		33	42.9
	Flexion contractures		7	9.1
Gastrointestinal	GERD		12	15.6
	Dyspepsia		6	7.8
	Dysphagia		7	9.1
Cardiac	Cardiomyopathy		5	6.5
	PAH		18	23.4
	MI		2	2.6
ILD			53	68.8
ILD patterns on HRCT	NSIP		24	31.2
	UIP		15	19.5
	Fibrosing NSIP		3	3.9
	Indeterminate		3	3.9
	N/A		7	9.1
Pattern of cDMARD				
Initial treatment	MTX		18	23.4
	AZA		11	14.3
	CYC		4	5.2
	MMF		41	53.2
	Tocilizumab		1	1.3
Addition of a new medicine	Cyclophosphamide		1	1.3
	RTX		7	9.1
	RTX + Mycophenol		3	3.9
	Mycophenol		7	9.1
	Azathioprine		1	1.3
Mean dose of prednisolone	5mg		38	49.4
	7mg		6	7.8
	10mg		10	13
	Off steroids		21	27.3
Outcome as per physician global assessment	Improved		7	9.1
	Stable		44	57.1
	Active		20	26
	Worsening		2	2.6
	Death		1	1.3

Table II: Stratification of clinical presentations and organ involvement between males and females with scleroderma.

Variables	Overall			Females			Males		
	lcSSc n (%)	dcSSc n (%)	p-value*	lcSSc	dcSSc	p-value*	lcSSc	dcSSc	p-value*
Age (years) (median (IQR))	42 (13)	33 (18)	0.09**	42 (13)	33 (17)	0.21	36 (26)	31 (23)	0.34
Onset disease age (years) (median (IQR))	34 (15)	27.5 (18)	0.13**	35 (14)	27 (19)	0.77	22 (23)	28 (19)	0.34
Disease duration (years) (median (IQR))	5 (4)	5.5 (6)	0.78**	5 (4)	6 (7)	0.87	3.5 (17)	4 (4)	0.32
Raynaud's phenomenon	33 (94.3)	37 (88.1)	0.45	29 (93.5)	33 (89.2)	0.53	4 (100)	4 (80)	0.34
Digital pits	11 (31.4)	17 (40.5)	0.48	9 (29)	15 (40.5)	0.32	2 (50)	2 (40)	0.76
Digital ulcers	11 (31.4)	21 (50)	0.11	9 (29)	18 (48.6)	0.1	2 (50)	3 (60)	0.76
Gangrene	4 (11.4)	6 (14.3)	0.75	4 (12.9)	6 (16.2)	0.701	0	0	
Skin									
Sclerodactyly	31 (88.6)	40 (95.2)		27 (87.1)	35 (94.6)		4 (100)	5 (100)	
Muscoloskeletal									
Arthralgia	18 (51.4)	19 (45.2)	0.86	16 (51.6)	17 (45.9)	0.89	2 (50)	2 (40)	0.76
Arthritis	14 (40)	19 (45.2)		12 (38.7)	16 (43.2)		2 (50)	3 (60)	
Flexion contractures	3 (8.6)	4 (9.5)		3 (9.7)	4 (10.8)		0	0	
Gastrointestinal									
GERD	6 (17.1)	6 (14.3)	0.72	5 (16.1)	6 (16.2)	0.66	1 (25)	0	0.16
Dyspepsia	3 (8.6)	3 (7.1)		3 (9.7)	2 (5.4)		0	1 (20)	
Dysphagia	4 (11.4)	3 (7.1)		4 (12.9)	3 (8.1)				
Cardiac									
Cardiomyopathy	3 (8.6)	2 (4.8)		3 (9.7)	2 (5.4)		0	0	0.71
PAH	11 (31.4)	7 (16.7)		10 (32.3)	6 (16.2)		1 (25)	1 (20)	
ILD	22 (62.9)	31 (73.8)	0.3	21 (67.7)	28 (75.7)	0.47	1 (25)	3 (60)	0.29

**Chi-square or Fisher's exact test; **Mann Whitney U-test; IQR: Interquartile range.*

RESULTS

Of the 77 patients, 9 (11.7%) were male and 68 (88.3%) were female, with a female-to-male ratio of 7.6:1. The mean age of the patients at presentation was 37.9 ± 11.2 years. Those with diffuse scleroderma were much younger (36 ± 11.3) years than those with limited scleroderma (40.2 ± 10.7) years. The general demographic and clinical characteristics of the patients are represented in Table I.

Table II compares the limited and the diffuse subtypes. In the limited subtype, 4 (11.4%) were males and 31 (88.6%) were females, whereas in the diffuse subtype, 5 (11.9%) were males and 37 (88.1%) were females. Concerning the initial presenting symptom in all patients, Raynaud's phenomenon was the most prevalent, with 33 (94.3%) in the lcSSc and 37 (88.1%) in the dcSSc subset. Additionally, no significant variance was noted between the two subsets. Further, when stratified, no significant gender differences in clinical manifestations and organ involvement in SSc patients were found.

DISCUSSION

SSc, though rare, carries a higher mortality rate and profoundly affects the quality of life[8] compared to other musculoskeletal disorders. Within the spectrum of SSc subtypes, dcSSc stands out as a major concern characterised by rapid progression and early involvement of vital organs such as the lungs, heart, and kidneys, posing life-threatening risks.

In the current study, a higher frequency of systemic sclerosis was noted among women compared to men. The study included 9 (11.7%) male and 68 (88.3%) female patients, resulting in a female-to-male ratio of 7.6:1. This observation aligns with the findings of Alam *et al*., who also reported a female predominance with a female-to- male ratio of 7.4:1.[9] Conversely, studies by Coi *et al*. in Italy,[10] and El Basel and Khalil among Egyptian patients[11] reported lower female-to-male ratios of 6.5:1, and 4.3:1, respectively, differing from the results of this research. Other investigations on systemic sclerosis patients have also shown a female preponderance, but with even higher female-to-male ratios compared to this study, such as those conducted by Elbraky *et al*.,[12] Asif *et al*.,[1] and Horimoto *et al*.,[13] which reported female-to-male ratios of 14:1, 16:3, and 28.6:1, respectively.

In this study, the average age of disease onset was found to be 30.69 ± 11.09 years, with specific ages of 32.6 ± 10.5 years for lcSSc and 29.1 ± 11.5 years for dcSSC subtypes. In contrast, Hughes and Harrick. indicated an onset age range of 55-69 years,[14] while Li *et al*. reported an average onset age of 48 years.[15]

Regarding the distribution of disease subtypes, the present study demonstrated a higher prevalence of the diffuse scleroderma subtype. Out of 77 patients, 42 (54.5%) were diagnosed with dcSSc, while 35 (45.5%) had lcSSc. These findings align with Khaliq *et al*.[16] and Asif *et al*.[1] who reported a higher incidence of 55% and 58% dcSSc compared to 55% and 38% lcSSc, respectively. However, Li *et al*. found that 65.6% of patients had limited scleroderma in their investigation.[15] Additionally, El Basel and Khalil reported that 61 (81.3%) patients had limited scleroderma, while 14 (18.7%) patients had diffuse scleroderma, resulting in a diffuse-limited ratio of 1:4.3.[11]

Raynaud's phenomenon, the predominant feature of this condition, was identified in 90.9% of patients in this study. Li *et al*. reported an incidence of 88.5%,[15] while Khaliq *et al*. observed a 100% prevalence in their research.[16] Secondary complications such as digital pitting and digital ulcers, arising from prolonged Raynaud's phenomenon, were noted in 36.4% and 41.6% of individuals, respectively. These rates were lower compared to the findings by Khaliq *et al*., who reported frequencies of 89% and 82%, respectively. Among gastrointestinal symptoms, GERD (15.6%) was the most prevalent, followed by dysphagia (9.1%) and dyspepsia (7.8%). These results showed a notably lower occurrence compared to

earlier research by Khaliq *et al*. where dysphagia ranged from 21.8 to 87%, and GERD was reported at 38%.[16]

In the present study, ILD was detected in 68.8% of individuals, with a higher prevalence in dcSSc (73.8%) compared to lcSSc (62.9%). This trend is consistent with prior research indicating a greater incidence of ILD in the diffuse subtype of scleroderma. Interestingly, Khaliq *et al*. noted a substantial occurrence of ILD in lcSSc patients as well, possibly due to the delayed onset of ILD in this subset of patients. The tertiary care setting of their patient cohort suggests that these individuals had been living with the disease for an extended period, leading to the development of various disease complications.[16]

The study's findings indicated that non-specific interstitial pneumonia (NSIP) was the most common form of ILD, accounting for 31.2% of cases, with usual interstitial pneumonia (UIP) representing 19.5% and fibrosing non-specific interstitial pneumonia (Fibrosing NSIP) 3.9% only. In contrast, Jafri *et al*. reported idiopathic pulmonary fibrosis (IPF) as the predominant ILD at 38.8%, followed by non-specific interstitial pneumonitis (NSIP) at 15.1%.[17] Similarly, Zubairi *et al*. identified idiopathic pulmonary fibrosis (IPF) in 40.4% of patients and non-specific interstitial pneumonia in 19.7% of patients.[18]

This study has certain limitations. Firstly, being conducted at a single tertiary care hospital with a small sample size could affect the generalisability and reliability of the results to different populations and settings. Secondly, potential ethnic or geographic influences on disease subsets and organ involvement patterns in systemic sclerosis were not adequately addressed in the study. Therefore, future research should incorporate multi-centre studies and take into account these factors for a more thorough comprehension.

CONCLUSION

Systemic sclerosis in the present population exhibits a higher prevalence among females, with a slightly elevated proportion of individuals having the diffuse type of the disease. Raynaud's phenomenon emerged as a prominent initial manifestation across subsets, emphasising its importance in early disease recognition. Importantly, the findings of this study suggest that gender does not significantly influence the clinical manifestations or organ involvement in SSc.

DISCLOSURE:

This paper was presented in the 26th Asia-Pacific League of Associations for Rheumatology Congress (APLAR), held in Suntec, Singapore from 21 to 25 August 2024.

ETHICAL APPROVAL:

The Institutional Ethical and Review Board of Central Park Medical College and Teaching Hospital gave approval for this study.

PATIENTS' CONSENT:

The participants provided informed and written consent for the study, ensuring confidentiality and adherence to ethical guidelines outlined in the Declaration of Helsinki.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

UA: Design of the work, data collection, analysis, and drafting of the work.
MAS, MRH, MA, SUD, HYQ: Design of the work and data analysis.
All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the work.

REFERENCES

1. Asif S, Khan A, Faiq M, Din ZU, Zahoor S, Haroon M. Clinical and serological characteristics of systemic sclerosis: Experience of a tertiary care center in Pakistan. *Arch Rheumatol* 2021; **36(4)**:587-94. doi: 10.46497/ArchRheumatol.2021.8701.
2. Pope JE, Denton CP, Johnson SR, Codina AF, Hudson M, Nevskaya T. State-of-the-art evidence in the treatment of systemic sclerosis. *Nat Rev Rheumatol* 2023; **19(4)**:212-26. doi: 10.1038/s41584-023-00909-5.
3. Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: A comprehensive systematic review and meta-analysis. *Rheumatology (Oxford)* 2021; **60(7)**:3121-33. doi: 10.1093/rheumatology/keab190.
4. Volkmann ER, Andreasson K, Smith V. Systemic sclerosis. *Lancet* 2023; **401(10373)**: 304-18. doi: 10.1016/S0140-6736(22)01692-0.
5. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, *et al*. The registry of the German network for systemic scleroderma: Frequency of disease subsets and patterns of organ involvement. *Rheumatolology* 2008; **47(8)**:1185-92. doi: 10.1093/rheumatology/ken179.
6. de Angelis R, Ferri C, Giuggioli D, Bajocchi G, Dagna L, Randone SB, *et al*. Systemic sclerosis sine scleroderma: Clinical and serological features and relationship with other cutaneous subsets in a large series of patients from the national registry 'SPRING' of the Italian society for rheumatology. *RMD Open* 2023; **9**:e002890. doi: 10.1136/rmdopen-2022-002890.
7. Sobolewski P, Maslinska M, Wieczorek M, Lagun Z, Malewska A, Roszkiewicz M, *et al*. Systemic sclerosis - multidisciplinary disease: Clinical features and treatment. *Reumatologia* 2019; **57(4)**:221-33. doi: 10.5114/reum.2019.87619.
8. Khanna D, Lescoat A, Roofeh D, Bernstein EJ, Kazerooni EA, Roth MD, *et al*. Systemic sclerosis–associated interstitial lung disease: How to incorporate two food and drug administration- approved therapies in clinical practice. *Arthritis Rheumatol* 2022; **74(1)**: 13-27. doi: 10.1002/art.41933.
9. Alam F, Abdulaziz HM, Haq IU, Mahdy SM, Siam ARM, Chandra P, *et al*. Characteristics of patients with systemic sclerosis living in Qatar. *Qatar Med J* 2019; **2019(3)**:16. doi: 10.5339/qmj.2019.16.
10. Coi A, Barsotti S, Santoro M, Almerigogna F, Bargagli E, Caproni M, *et al*. Epidemiology of systemic sclerosis: A multi-

database population-based study in Tuscany (Italy). *Orphanet J Rare Dis* 2021; **16(1)**:90. doi: 10.1186/s13023-021-01733-4.

11. El Basel M, Khalil N. Disease characteristics of systemic sclerosis among Egyptian patients. *Kasr Al Ainy Med J* 2015; **21(2)**:41-6. doi: 10.4103/1687-4625.162378.
12. Elbraky FM, Amailaf IA, Alsaeiti K. Demographic characteristics and clinical manifestations of systematic sclerosis in Benghazi, Libya. *Ibnosina J Med Biomed Sci* 2020; **12(2)**: 118-22. doi: 10.4103/ijmbs.ijmbs_36_20.
13. Horimoto AMC, Matos ENN, da Costa MR, Takahashi F, Rezende MC, Kanomata LB, *et al*. Incidence and prevalence of systemic sclerosis in Campo Grande, State of Mato Grosso do Sul, Brazil. *Rev Bras Reumatol* 2017; **57(2)**:107-14. doi: 10.1016/j.rbre.2016.09.005.
14. Hughes M, Herrick AL. Systemic sclerosis. *Br J Hosp Med (Lond)* 2019; **80(9)**:530-6. doi: 10.12968/hmed.2019.80.9.530.
15. Li H, Zhang X, Yu L, Shang J, Fan J, Feng X, *et al*. Comparing clinical characteristics of systemic sclerosis with or without interstitial lung disease: A cross-sectional study from a single center of the Chinese rheumatism data center. *Front Med (Lausanne)* 2022; **9**:1061738. doi: 10.3389/fmed.2022.1061738.
16. Khaliq T, Aziz W, Farooqi A. Spectrum of systemic sclerosis in patients presenting to a tertiary care hospital in Pakistan. *Pak Armed Forces Med J* 2014; **64(4)**:591-5. https://www.pafmj.org/PAFMJ/article/view/1650/1414.
17. Jafri S, Ahmed N, Saifullah N, Musheer M. Epidemiology and clinico-radiological features of interstitial lung diseases. *Pak J Med Sci* 2020; **36(3)**:365-70. doi: 10.12669/pjms.36.3.1046.
18. Zubairi ABS, Hassan M, Shahzad T, Sarwar S, Abbas A, Ahmad H, *et al*. Spectrum of interstitial lung disease from a tertiary care hospital in Karachi. *J Pak Med Assoc* 2017; **67(7)**:1065-9.