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ORIGINAL ARTICLE

Unique clinical and autoantibody profile of a large Asian Indian cohort of scleroderma—do South Asians have a more aggressive disease?

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Abstract

Aim and methods A single-centre retrospective study was conducted using electronic medical records (EMR) of inpatients and outpatients with the diagnosis of "scleroderma" or "systemic sclerosis" visiting our clinic over the preceding 5 years.

Results A total of 327 patients' charts met our selection criteria; 301 were females. The median (IQR (inter quartile range)) age at onset of first non-Raynaud's symptom was 34.67 (27–43) years and median (IQR) disease duration prior to presentation to our department was 2.5 (1–5) years. Of these, 310 (94.8%) belonged to diffuse systemic sclerosis variety, 13 (4%) had limited systemic sclerosis, and 4 (1.2%) were of sine scleroderma type. A total of 289/302 (95.7%) patients were positive for ANA; of them, 245/327 (74.9%) were Scl-70 antibody-positive and 4% were CENP antibody-positive. Interstitial lung disease (ILD) was present in 288/327 (88.1%) patients. Among patients with available baseline forced vital capacity (FVC) data, 20% had a normal lung function and 28.4% had severe restriction. Pulmonary hypertension as assessed by echocardiography was present in 8.1% of patients. A significant association of Scl-70 antibody positivity with the presence of interstitial lung disease (ILD) ($p = 0.000$) and pulmonary hypertension ($p = 0.035$) was seen. On the other hand, presence of CENP antibody showed a protective trend against muscle weakness and/or muscle enzyme elevation ($p = 0.052$). Presence of arthritis was protective against development of digital ulceration ($p = 0.021$) and PAH (0.004). Patients younger than 40 years of age had significantly higher frequency of Scl-70 positivity ($p = 0.038$), whereas CENP antibody positivity was more likely in those aged > 40 years ($p = 0.002$).

Conclusion Younger age of onset and high prevalence of Scl-70 antibody are unique South Asian features common with large Indian, Thai, and Chinese series. High prevalence of ILD is a feature common to Indian and Chinese series. Strong correlation of Scl-70 antibody with younger age and pulmonary hypertension were unique features of our cohort.

Key Points

- *Asian Indian scleroderma patients are younger by 2 decades compared to Caucasian series.*
- *Higher prevalence of Scl-70 antibody, its association with young age, interstitial lung disease and pulmonary hypertension are features of our cohort.*
- *High prevalence of interstitial lung disease (88.1%) was noted ; among those with baseline spirometry data (141/327), two thirds(66%) had moderate to severe restriction.*
- *Younger age at onset, higher prevalence of Scl-70 antibody are features common to other Indian, Thai and Chinese series.*

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Keywords Anti-Scl-70 antibody · Interstitial lung disease · Pulmonary arterial hypertension · Scleroderma · Younger

Introduction

Systemic sclerosis is a rare systemic autoimmune disorder. Its prevalence has been estimated to be about 443 cases/million population in North American studies [1]. Not only does incidence, prevalence, and clinical and autoantibody profile of scleroderma vary as per geography, so does the clinical and autoantibody profile of various cohorts. Large epidemiological studies on prevalence and clinical profile are nonexistent in India. However, single referral centre–based clinical and serological descriptions from India reflect variable figures [2–7].

There are two epidemiological studies on scleroderma from Japan [8, 9], multicentre studies from various Asian countries [10–13]. We undertook a retrospective study to characterize the clinical and autoantibody profile of scleroderma patients visiting our centre, a large tertiary care centre in southern India.

Materials and methods

Data of inpatients and outpatients with the diagnosis of "scleroderma" or "systemic sclerosis" who visited the department of Clinical Immunology & Rheumatology, Christian Medical College, Vellore, between 2008 and 2013 were retrieved from the electronic medical records (EMR) as well as scanned medical reports of patients.

Patients were classified as diffuse and limited scleroderma based on American College of Rheumatology preliminary classification criteria (1980) for the classification of systemic sclerosis. Diagnosis of sine scleroderma was based on absence of skin involvement with presence of visceral involvement typical of systemic sclerosis. Patients with localized scleroderma (morphea and linear scleroderma), mixed connective tissue disease, and other overlap connective tissue diseases as well as undifferentiated connective tissue disease were excluded from the study.

Clinical data were retrieved from the charts and electronic medical records maintained by medical records department; laboratory profile, radiological images, pulmonary function testing data, and echocardiography data were collected from EMR of our institute. Approval from ethics committee obtained from Institutional review board, Christian Medical College, Vellore, India. Since this study is a retrospective chart review, consent for participation in the study has not been obtained.

Serological positivity was recorded as per cutoffs defined by the laboratory. Antinuclear antibody (ANA) is tested in our laboratory by indirect immunofluorescence (IIF) using Euro immune kits. Anti-topoisomerase (ATA-1/Scl-70), anti-centromere (CENP) antibody, and U1 ribonucleoprotein (U1RNP) antibody were also tested by Euro immune ELISA kits. The diagnosis of interstitial lung diseases was made on the basis of high-resolution computed tomography (HRCT) of the chest reported by radiologists at our institute in majority of the cases. Only for occasional patients, the diagnosis was based on clinical examination findings and plain chest radiograph (CXR). Spirometry and diffusion capacity of lung for carbon monoxide [DLCO] were performed according to standard guidelines of the pulmonary function laboratory. Echocardiography parameters as reported by our cardiology department were retrieved. Right ventricular systolic pressure (RVSP) ≥ 40 mmHg as per echocardiography was considered as an evidence for presence of pulmonary hypertension.

Statistical methods

Data was analysed using chi-square test for statistical significance between groups. Association between autoantibody profile and organ manifestations was evaluated using Student's *t* test and logistic regression analysis. STATA software version 14 was used for analysis.

Results

A total 560 charts were screened, of which 327 patients' charts met our selection criteria mentioned under methodology. Of these, 310 (94.8%) belonged to diffuse systemic sclerosis variety, 13 (4%) had limited systemic sclerosis and 4 (1.2%) were of sine scleroderma type. Of the 327 patients, 301 were females with a gender ratio of 11:1. The median (IQR (inter quartile range)) age at onset of first non-Raynaud's symptom was 34.67 (27–43) years and the mean (SD (standard deviation)) age of the cohort was 35.08 (11.3) years. Median (IQR) disease duration prior to presentation to our department was 2.5 (1–5) years.

Baseline clinical profile is represented in Table 1 and Fig. 1. Skin tightness and Raynaud's phenomenon were the commonest presenting complaints. Among other complaints, arthralgia /arthritis as well as respiratory symptoms in the form of breathlessness and cough were the most prevalent ones. Among gastrointestinal symptoms, retrosternal burning sensation was the commonest, followed by dysphagia.

Laboratory data (Table 2)

Anaemia was present in 54.3% of individuals; symptomatic muscle weakness was documented in 13.7% of individuals, while raised CPK was present in 13.4% of the cases. Proteinuria and raised creatinine was present in 6.8% and

Table 1 Baseline demographics

Baseline demography/clinical manifestations	Frequency number (%) $N = 327$
Mean age (± SD) in years	35.08 (± 11.3)
Gender (F:M)	301:26
Median disease duration (IQR) (years)	2.5 (1–5)
Diffuse systemic sclerosis (*n* (%))	310 (94.8%)
Limited systemic sclerosis (*n* (%))	13 (4%)
Sine scleroderma (*n* (%))	4 (1.2%)

1.2% of the patients, respectively. Clinical hypothyroidism was found in 8.3% of the cases.

Autoantibody profile (Table 2)

A total of 289/302 (95.7%) patients were positive for ANA; of them, 245/327 (74.9%) were Scl-70 antibody-positive (i.e. 64/327 (19.6%) were Scl-70 negative); 4% were CENP antibody-positive; 3 patients were dual positive, of which 2 of them were positive for both Scl-70 and CENP and one individual was positive for CENP as well as Jo-1 antibody. Among the patients who were diagnosed diffuse systemic sclerosis, 95.5% were ANA-positive; 81% were Scl-70 antibody-positive, 1.7% were CENP antibody-positive, and 7.6% of the patients fulfilling classification criteria for scleroderma were U1RNP antibody-positive, even though they did not belong to MCTD category. All patients with the diagnosis of limited systemic sclerosis were ANA-positive; 71.4% of them were CENP antibody-positive, and 14.3% of patients with limited scleroderma were Scl-70 antibody-positive. All the 4 patients with the diagnosis of sine scleroderma were ANA- and Scl-70-positive.

Organ involvement: (Fig. 2)

Skin

MRSS data at baseline was available for 63 patients. Mean (SD) MRSS score was 20.02 (12.69) and the median (IQR) score was 16 (8.5–25).

Lung

Of the whole cohort, 193/327 (59%) had presented with breathlessness and 173/193 (90%) had breathless due to interstitial lung disease (ILD); 10/173 (5.8%) had associated PAH as well. Among the rest without ILD, 2 had breathlessness due to PAH.

Pulmonary function testing (Fig. 3)

Forced vital capacity (FVC) data at baseline was available for 151/339 (44.5%) patients. Ten of these patients had no ILD at baseline as ascertained by HRCT. Of the 141 patients with ILD who had a baseline FVC data, 28/141 (20%) had a normal FVC (≥ 80% predicted) at

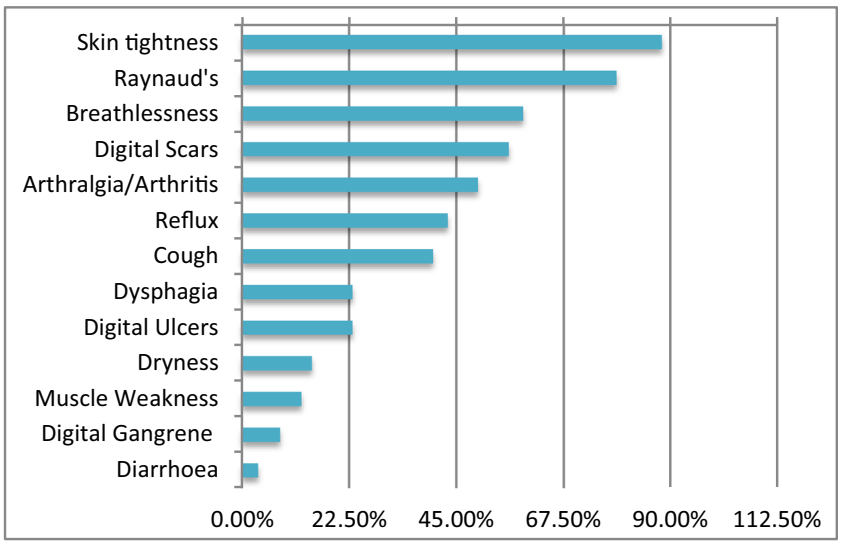

Fig. 1 Frequency of clinical manifestations at presentation

Table 2 Baseline immunological and laboratory parameters

Laboratory and autoantibody profile (Number of patients for whom data available)	Number (%)
ANA (286)	274 (95.8)
Scl-70 (3150	243 (77.1)
CENP (315)	15 (4.8)
Anaemia Hb g% M < 13; F < 12 (324)	179 (55.2)
ESR > 40 (272)	111 (40.8)
Creatinine > 1.4 (321)	4 (1.2)
CPK elevation (239)	32 (13.4)
Subclinical hypothyroidism (252)	58 (23)
Clinical hypothyroidism	21 (8.3)
Hyperthyroidism	6 (2.4)
B12 < 200 (71)	15 (2.1)
Proteinuria (24 h UP > 150 mg; UP/UC > 0.15) (209)	21 (6.8)

baseline, 20/141 (14.2%) had mild restriction (70–79% predicted), 53/141 (37.6%) had moderate restriction (50–69% predicted), and 40/141 (28.4%) had severe restriction (< 50% predicted) (Fig. 3). DLCO values at baseline were available for 82 individuals. Five of them had no interstitial lung disease. Of the remaining 77 patients, 6/77 (7.8%) had normal (≥ 80% predicted), 2/77 (2.6%) had mild (70–79% predicted), 16/77 (20.8%) has moderate (50–69% predicted) and 53/77 (68.8%) had severe (< 50% predicted) reduction in DLCO at baseline [14].

HRCT

Interstitial lung disease was present in 288/327 (88.1%) patients, 280 of them were diagnosed by HRCT and the remaining 8 by CXR and clinical findings. Of those with HRCT-diagnosed ILD, 47.9% had NSIP pattern, 14.7% had UIP pattern, and 14.1% had no specified pattern as per radiologists' reports. Forty (14.3%) patients had a HRCT diagnosis of early ILD; 17 of them had a baseline spirometry data as well. Of these 17 patients, almost equal number (9 and 8) had normal and mild restrictive defects, respectively by spirometry.

Vasculopathy

Pulmonary vasculature

Pulmonary hypertension as assessed by echocardiography was present in 18/223 (8.1%) patients. Sixteen of them had diffuse scleroderma; 1 each had limited and sine scleroderma.

Digital ulceration and gangrene

History of digital ulceration and gangrene was documented in 76/327 (23.2%) and 26/327 (8%) of the patients, respectively; 183/327 (56%) were noted to have digital tip scars by the clinician.

Gastrointestinal involvement

Retrosternal burning was present in 141/327 (43.1%), dysphagia in 76/327 (23.2%), and diarrhoea in 11/327 (3.4%) of the patients. Dry mouth was present in 48/327 (14.7%) of the patients. Of the 299 individuals imaged by HRCT, 205 (72.2%) had CT features of dilated oesophagus.

Musculoskeletal

Muscle weakness was a presenting feature in 41/327 (12.5%) of the patients. Laboratory evidence of raised creatinine

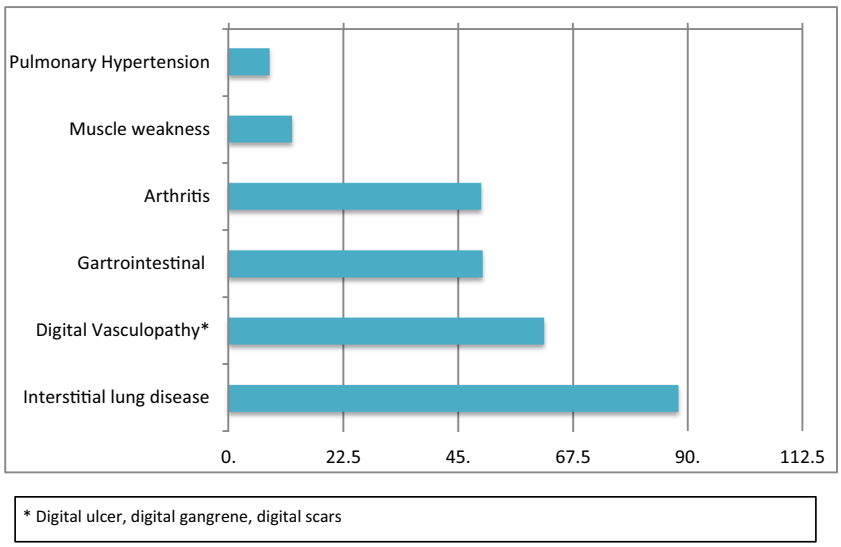

Fig. 2 Prevalence of organ involvement in our scleroderma series. Asterisk means digital ulcer, digital gangrene, and digital scars

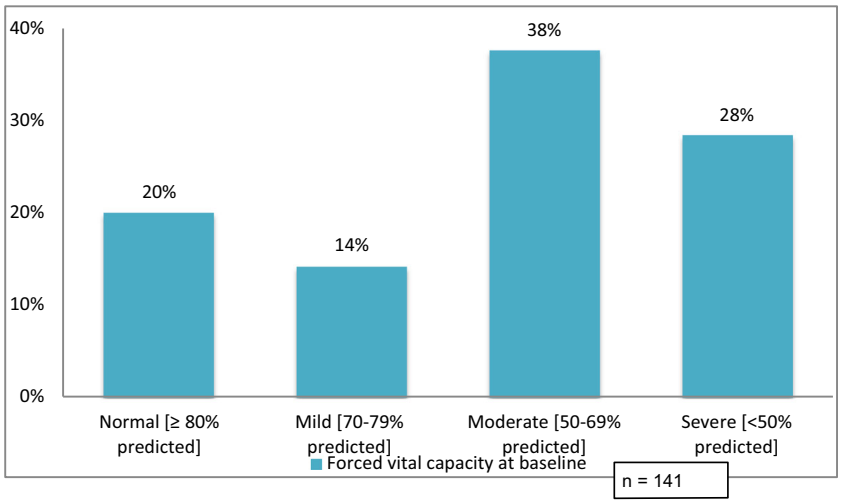

Fig. 3 Pulmonary function testing and related data

phosphokinase (CPK) was documented in 32/327 (9.8%) of the patients. Arthralgias/arthritis was noted in 169/327 (51.7%) of the patients.

Other organ involvement

Scleroderma renal crisis was diagnosed in 2 patients; 1 of these 2 patients had interstitial nephritis, in addition.

Cardiac involvement was seen in 5 patients: 1 each had right ventricular hypokinesia, atrial fibrillation, complete heart block, right heart failure due to PAH, and congestive cardiac failure. Documented mild-to-moderate pericardial effusion was seen in 10 patients. All had ILD except 1 of them. Of these patients, 2 had documented myositis and 1 of them had pulmonary hypertension, in addition. Involvement of liver was found in 3 patients; primary biliary cirrhosis, sclerosing cholangitis, and chronic liver disease were found in 1 patient each. A single patient was diagnosed to have bacterial overgrowth syndrome.

Malignancy

Adenocarcinoma of the lung with metastasis was diagnosed in one patient.

Treatment

Majority of our patients received upfront second line immunosuppressive medications in addition to steroids. Mycophenolate mofetil (MMF) was started in 181/327 (55.5%) patients, azathioprine in 78/327 (24%), and pulse cyclophosphamide in 19/329 (5.8%) of the patients. The commonest indication for patients to be on immunosuppressive medications was interstitial lung disease. Among the rest, 4 (1.2%) were on methotrexate, 6 (1.8%) were initiated on D-penicillamine, and 28 (8.6%) did not receive any second-line immunosuppression.

Associations of clinical and autoantibody profile (Table 3)

A significant association of Scl-70 antibody positivity with the presence of ILD ($p = 0.000$) and CENP antibody positivity with the absence of ILD ($p = 0.000$) were noted. Scl-70 antibody positivity, in addition, was also associated with presence of pulmonary hypertension ($p = 0.035$). On the other hand, presence of CENP antibody showed a protective trend against muscle weakness with or without muscle enzyme elevation ($p = 0.052$).

Regression analysis showed a trend towards association between Scl-70 antibody positivity and presence of ILD (OR 1.89 (− 0.06 to 3.59; $p = 0.058$)) and presence of GI involvement (OR 1.86 (− 0.49 to 1.98; $p = 0.063$)).

Table 3 Association of autoantibody profile with clinical manifestation

Parameter	Scl 70 $n = 243$ p value	CENP $n = 15$ p value
Digital vasculopathy	153 (0.477)	Not analysed because of small numbers
GI	122 (0.390)	8 (0.724)
Arthritis	125 (0.897)	6 (0.398)
Pulmonary HTN	10 (0.035)	1 (0.809)
ILD	224 (0.000)	3 (0.000)
Muscle weakness	47 (0.985)	0 (0.052)

Table 4 Association of age at onset with clinical manifestations and autoantibody profile

Parameters (Present, absent)	Age at onset < 40 years ($n = 223$)	Age at onset > 40 years ($n = 104$)	p value
Scl-70	174	67	0.038
ACA	5	10	0.002
U1RNP	21	4	0.049
ANA	184	88	0.59
Muscle weakness ≠ − raised CPK	42	21	0.771
Arthritis	110	59	0.212
Digital ulceration ≠ − digital pits	86	33	0.23
Gangrene	16	10	0.447
ILD	197	83	0.133
Pul HTN	12	6	0.874

Other clinical associations

Patients younger than 40 years of age had significantly higher frequency of Scl-70 positivity ($p = 0.038$), whereas CENP antibody positivity was more likely in those aged > 40 years ($p = 0.002$) (Table 4).

Presence of arthritis was protective against development of digital ulceration ($p = 0.021$) and PAH (0.004) (Table 5).

Discussion

Our study describes the clinical profile of a large cohort of scleroderma patients from the Indian subcontinent. There have been few single-centre-based Indian studies; however, we looked at only those data published by rheumatology departments with at least 100 patients in series (Table 6) for comparison [2]. Sharma et al. and Ghosh et al. have looked into dermatological perspectives of the disease [3, 4]. Older studies have been omitted from such comparisons, because of smaller number and lack of complete immunological profile [5, 7].

Earlier age at onset (< 35 years of age) is a striking finding in our cohort in common with other Indian series (30–35 years) on scleroderma [2–4]. Large scleroderma cohorts from China, Japan, and Thailand are a decade younger as compared with Caucasian cohorts. In the study by Steen et al., African-Americans scleroderma patients had a younger age at onset compared with Caucasians [11]. Hence, age at onset of scleroderma has a significant racial variation with South Asians being decade or two younger than their Caucasian counterparts. Frequency of Raynaud's phenomenon was also lesser (78.6%) as compared with the north Indian cohort (92.9%) [4] and the rest of the world literature (96–99%) (10–14), but this figure was similar to the western Indian cohort (76.5%) [2]. Whether this lower figure is a true reflection or due to the combined effect of darker skin complexion and warmer climate is not clear.

The prevalence of ILD is higher (88%) in our cohort, which is comparable to the western Indian data (88.2%), the north Indian data (85.8% abnormal pulmonary function testing (PFT) in north Indian data) [2, 4], and the Chinese data (78%) [13]. However, it is much higher as compared with the rest of the published literature (33–54%) [10–12, 15]. According to the study by Schurawitzki et al., on patients of systemic sclerosis with HRCT data in all patients, 91% had some abnormality suggestive of ILD [16]. Of our HRCT-diagnosed ILD patients with baseline spirometry data, 20% had a normal FVC at baseline. Little over a third (37.6%) of patients had moderate and over a fourth (28.4%) of the patients had severe restrictive lung function in spirometry. In a large scleroderma cohort of Caucasian and African-American ancestry described by Steen et al., 27% patients had moderate and 13% had severe restrictive PFT findings [17]. Since half of our cohort did not have a baseline spirometry data, and due

Table 5 Association of arthritis with other clinical features

Clinical features.	Arthritis ($n = 169$)	No arthritis—($n = 143$)	p value
ILD	126	121	0.81
PAH	6	13	0.021
Digital ulceration/pits	50	62	0.004
Gangrene	11	13	0.43
Muscle weakness	39	19	0.17
Oesophageal involvement	114	94	0.88

Table 6 Comparison of data from published literature on scleroderma in different ethnicities series

Variable.	Current study Janardana et al. (single-centre)	Asian Indian Pradhan et al. [2] (single-centre)	Japanese Hashimoto et al. [15] (single-centre)	Caucasian EUSTAR Meier et al. [10] (multicentric)	Hispanic Skare et al. [12] (single-centre)	Black Steen et al. [11] (multicentric)	Chinese Wang et al. [13] (multicentric)
Number	327	110	405	7655	66	203	419
Age of onset in years (mean ± SD)	36.26 ± 10.8	34.7 ± 10.7	46 ± 0.8	54.3 ± 13.8	51.35 ± 13.72	38.4 ± 14.3	NA
Gender F:M	88.4:11.6 (301:26)	91:9 (100:10)	92.8:7.2 (376:29)	86:14 (6591:1064)	92.4:7.6 (61:5)	76:24 (155:45)	4.9:1
Median (IQR)/mean (SD) disease duration (years)	2.5 (1–5)	3.7 (0.5–12)	2 ± 0.4 (0–44)	NA	11.08 ± 8.56	2.97 (1.27–8.04)	7.3 (1–32)
Diffuse vs limited (%)	94.8 vs 4	40.9 vs 29.1	NA	33.3 vs 66.7	62.1 vs 21.2	43	59.7 vs 40.3
Sine scleroderma (%)	1.2	NA	NA	NA	3	NA	NA
Overlap (%)	0	30	NA	24	13.6	16	NA
Raynaud's (%)	78.6	76.5	NA	96.3	98.4	99	NA
Vasculopathy in (%)[b]	61.8	23.5	NA	36	30.6	43	NA
Arthritis (%)	49.5	39.1	NA	15	44.4	85	NA
Muscle weakness in (%)	12.5	NA	NA	25	19.04	27	NA
GI involvement (%)	49.8	7.3	46.2	67.3	58.73	70	NA
Cardiac (pericardial) (%)	1.5 (3.1)	13.6	19.2	8.6	27 (4.7)	20	NA
SRC (overall renal) (%)	0.6 (0.9)	(10.9)	2.7 (14.9)	(2.1)	1.58	(13)	NA
ILD (%)	88.1	88.2	48.4	51.9	41.2	54	78
PAH (%)	8.1	61.2	16	21.1	58.7	11	NA
ANA positivity (%)	95.7	85.5	95.5	93.4	92.4	NA	90.7
Scl-70 positivity (%)	74.9	62.7	23.5	36.8	17.8	25	59.9
CENP positivity (%)	4	22.7	35.9	32.3	33.3	17	13.4
RNP positivity (%)	7.6	NA	23.2	7.7	11.8	13	18

[a] NA—data not available

[b] Includes digital ulcer, gangrene, and digital tip scars

to referral centre bias in our cohort, it is not possible to conclude whether our scleroderma cohort has a greater prevalence of severe restrictive defect at baseline. EUSTAR database, the largest Caucasian scleroderma cohort, had 52% of its patients with lung fibrosis by HRCT, whereas only 32% of their cohort were having restrictive PFT findings [10].

We have found a higher prevalence of Scl-70 antibody (74.9%), similar to that described in Thai series (85.7%) [18] and Chinese series [13], and this figure is higher than that of any other published Indian series (62.7%) [2], as well as rest of the world literature (18–59.9%) [19, 20]. Our cohort has disproportionately higher frequency of diffuse disease subset, possibly because of referral bias; however, this cannot account for the higher serological positivity in our cohort. Higher prevalence may also be explained by geo-ethnic and genetic differences of our cohort.

Presence of Scl-70 antibody strongly correlated with ILD and pulmonary hypertension in our cohort. Scl-70 antibody positivity also tended to show an independent association with ILD on regression analysis. Independent association of Scl-70 antibody positivity and pulmonary hypertension was a unique feature of our cohort. This could be possibly due to PAH secondary to ILD, rather than primary vasculopathic process. CENP positivity had a negative association with ILD and muscle weakness. These findings were already established by earlier studies. Our series also noted associations between younger age at onset (< 40 years) and presence of Scl-70 antibody, whereas older age at onset was associated with CENP antibody positivity.

The prevalence of echocardiography-diagnosed PAH (8.1%) in our cohort is slightly lower as compared with published literature (11–21%). It may be possible that we may have missed few patients since a screening echocardiography was not done in a third of our patients (102/327). The prevalence of vasculopathy in the form of digital pits, active ulceration, and gangrene (23.2%, 56%, and 8%) in our cohort is comparable to that in other Indian series (ranging between 23.5 and 58.6%) as well as world literature (ranging between 36 and 44%).

Cardiovascular involvement in our cohort (1.5%) is also lower as compared with other Indian (13.6%) and global data (8.6–27%). It may be due to retrospective nature of the study and probable subclinical disease in some patients.

Scleroderma renal crisis/renal involvement was found only in 2 patients (0.6%) in our cohort, comparable with reports from Hispanic population (1.5%) [12] and EUSTAR registry data (2%) [10], but it is far lower than the figures from other Indian series (10.9%) [2] as well as other ethnicities across the globe (10.9–14.9) [11, 15].

Conclusion

Younger age of onset, higher prevalence of Scl-70 antibody, and interstitial lung disease are features of our cohort of scleroderma patients common with other published, large Indian series. Younger age at onset and higher prevalence of Scl-70 antibody positivity are a unique South Asian feature in common with large Chinese [21] and Thai series. Higher prevalence of ILD observed in common with Chinese and other Indian series [13].

Strong correlation of Scl-70 antibody with pulmonary hypertension and its association with younger age at onset is are other unique features of our cohort.

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Compliance with ethical standards

Disclosures None.

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