Original Article

Clinical and autoantibody profiles of systemic sclerosis patients: A cross-sectional study from North India

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Abstract

Objectives: This cross-sectional study was designed to assess the clinical profile and frequency of associated autoantibodies in all consecutive patients classified as systemic sclerosis (SSc) at Medanta—the Medicity Hospital, Gurgaon, India.

Methods: Between August 2017 and July 2019, we identified a total of 119 consecutive patients meeting the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 criteria for SSc and 106 patients consented to this study. Their clinical and serological data at the time of enrolment were analysed.

Results: Our cohort had a mean age at symptom onset of 40 ± 13 years with a median symptom duration of 6 years. We had 76 patients (71.7%) with interstitial lung disease (ILD), which was a higher proportion compared to European cohorts. 62 patients (58.5%) had diffuse cutaneous involvement which was significantly associated with anti-Scl70 antibodies ($p < 0.001$), digital ulcers ($p = 0.039$) and the presence of ILD ($p = 0.004$). 65 patients (61.3%) had anti-Scl70 and 15 patients (14.2%) had anti-centromere (anti-CENP) antibodies. Scl70 positivity was associated with the presence of ILD ($p < 0.001$) and digital ulcers ($p = 0.01$). Centromere antibodies had a negative association with ILD ($p < 0.001$), but was a risk factor for calcinosis ($p < 0.001$) and pulmonary arterial hypertension (PAH) ($p = 0.01$). The combination of diffuse cutaneous disease and Scl70 antibodies was the strongest predictor of ILD and digital ulcers ($p = 0.015$). sm/RMP, RNP68 and Ku antibodies correlated with musculoskeletal involvement ($p < 0.01$), while all seven of the patients with Pm/Scl antibodies had ILD. Renal involvement was noted in only two patients.

Limitations: A single-centre study may not capture the true prevalence of disease characteristics in the population. Referral bias for patients with diffuse cutaneous disease has been noted. Data on RNA-Polymerase antibodies have not been provided.

Conclusion: North Indian patients have some characteristic differences in disease phenotype as compared to their Caucasian counterparts with a larger proportion of patients presenting with ILD and Scl70 antibodies. Antibodies against Ku, RNP and Pm/Scl occur in a minority of patients, but may be associated with musculoskeletal features.

Keywords: Scleroderma, systemic sclerosis, autoantibodies, Indian, Interstitial lung disease

Plain Language Summary

We conducted this cross-sectional study to determine the clinical phenotypes and frequency of associated autoantibodies in systemic sclerosis patients at a tertiary-care centre. Hundred and six such patients consented to this study and had a mean age at symptom onset of 40 ± 13 years with a median symptom duration of 6 years. Around 71.7% of our patients had interstitial lung disease. Around 58.5% of our cohort had diffuse cutaneous involvement which was significantly associated with anti-Scl70 antibodies, digital ulcers and the presence of interstitial lung disease. The presence of anti-Scl70 antibodies was a risk factor for the presence of interstitial lung disease (ILD) and digital ulcers, while anti-centromere antibodies seemed to be negatively correlated with ILD, but were a risk factor for calcinosis and pulmonary arterial hypertension. The combination of diffuse

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cutaneous disease and Scl70 antibodies was the strongest predictor of ILD and digital ulceration. Patients with antibodies against RNP68, sm/RNP and Ku had significantly more musculoskeletal involvement. Renal involvement was noted in only two patients. We concluded that North Indian patients have some phenotypic differences as compared to their Caucasian counterparts with a larger proportion of patients presenting with ILD and Scl70 antibodies. The role of minor antibodies deserves special mention and future studies.

Introduction

Systemic sclerosis (SSc), or scleroderma, is an idiopathic systemic autoimmune disease characterized by the triad of vasculopathy, immune dysfunction and fibrosis.[1] The prevalence of SSc has been reported to be as high as 276 to 658 per million[2,3] in epidemiological studies from the United States of America (USA), while studies from Asia have reported lower prevalence rates of around 56 per million.[4] A study by Mintz *et al.* retrospectively analyzed data from ANA-positive patients in an Indian setting between 1996 and 2006 and estimated the prevalence to be around 120 per million population.[5]

The pathogenetic processes in SSc have been extensively studied and some autoantibodies seem to have strong associations with organ involvement. The two major phenotypic subtypes are based on the extent of skin involvement; data from various studies have supported the claim that the diffuse and limited cutaneous subtypes might be clinically distinct entities with differences in severity of organ involvement as well as their autoantibody associations. The most common disease-specific autoantibodies reported in patients are anti-Topoisomerase I (anti-Scl70) and anti-centromere antibodies (Anti-Centromere),[6] but other multiple autoantibodies have shown a greater association with SSc than with other autoimmune diseases.

There is a dearth of data from large cohorts in India that may help to uncover the true prevalence of SSc in the population and thus help to understand some of the geographic and ethnic differences in autoantibody profiles and phenotypes of patients noted from around the globe.[7] Being a rare disease with considerable heterogeneity in presentation, SSc leaves a rather large gap in the characterization of its autoantibody associations and correlation with clinical phenotypes. We designed this single-centre, cross-sectional study from Medanta—the Medicity Hospital, Gurgaon, India to study the clinical and serological characteristics of SSc patients and uncover any differences between patients of North India and those from other countries.

Materials and Methods

Study Design: This cross-sectional study was conducted at the Department of Rheumatology and Clinical Immunology at Medanta—the Medicity Hospital, Gurgaon, from August 2017 to June 2019.

Patient Details: We collected the data of all consecutive patients attending our outpatient or inpatient departments from August 2017 to June 2019, who were classified as SSc as per the American college of rheumatology/European league against rheumatism 2013 criteria[8] for clinical trials. We excluded pregnant females, patients less than 18 years of age and those who did not give consent to be included in this study.

Methodology: The patients were subjected to various predefined tests after obtaining informed and written consent. Demographic details, clinical features, laboratory parameters and available imaging reports of patients were analysed. Disease characteristics including disease duration and disease subtype, that is, limited cutaneous (lc) or diffuse cutaneous (dc) SSc, were recorded. Patients without skin involvement were included in the limited cutaneous group. Skin involvement was assessed by a modified Rodnan skin thickness score (mRSS) by a single assessor. Pulmonary involvement was assessed by high-resolution computed tomography (HRCT) of the thorax and, if present, further classified as non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) according to a trained radiologist. Joint disease was defined by history or current arthralgia/arthritis. Renal involvement was assessed by serum creatinine, urine routine and microscopy and presence of scleroderma renal crisis. Gastrointestinal involvement was assessed by the history of dyspepsia, abdominal bloating, dysphagia, or frequent diarrhoea. Oesophageal Manometry was performed in selected cases with upper gastrointestinal complaints. Vasculopathy was defined by the presence of digital ulcers, gangrene, Raynaud's phenomenon with at least a biphasic colour change in digits in response to cold exposure, or pulmonary hypertension (PH) in the absence of primary lung disease. Nailfold capillaroscopy was performed using a Video capillaroscope in selected patients. Myositis was defined by the presence of weakness and elevated muscle enzymes in the absence of other clinical or serological features suggestive of idiopathic inflammatory myopathy. Cardiovascular involvement was assessed by 2D echocardiography findings and a cut-off value of Pulmonary Arterial Systolic Pressure (PASP) above 35 mm Hg was kept as the definition of pulmonary hypertension. We defined anaemia in our population with a value of haemoglobin <12 mg/dL.

After the collection of blood samples, sera were stored at –80°C in aliquots until being tested. Anti-nuclear antibodies (ANA) were reported by the indirect immunofluorescence (IIF) technique on Hep-2 cells. Extractable Nuclear Antigen (ENA) Profile included testing for 25 autoantibodies with a line immunoassay (LIA) method using the BlueDiverQuantrix-Anti-nuclear antibodies25 Screen IgG kit from D-tek, Belgium and a value of 6 U/mL or less for each antibody was

considered as negative as per the prespecified cut-off value of this kit. Standard blood tests like complete haemogram, ESR, liver and renal function tests and creatine phosphokinase were carried out on all patients.

Statistical Analysis: Continuous quantitative data were presented in terms of means and standard deviation. Qualitative/categorical data were presented as absolute numbers and proportions. Cross tables were generated and chi-the square test was used to test associations between grouped variables. Statistical significance was set at $P < 0.05$. SPSS software Version 24.0 was used for statistical analysis.

Compliance with Ethical Standards: Patients were included in the study after taking informed consent. The study has been approved by Institutional Review Board at Medanta—— the Medicity, Gurgaon [MICR- 771/2017].

Results

During the defined study period, a total of 119 consecutive patients meeting the American college of rheumatology/ European league against rheumatism 2013 criteria for SSc were screened and their demographic and disease parameters were noted. Of these, 106 patients consented to be included in this study; their blood samples were collected for serology and they were all included in the final analysis.

Demographic Characteristics: The mean age at evaluation of the 106 patients was 47.57 ± 12.19 years with a median symptom duration of 6 years (IQR 3-10). The mean age at onset of symptoms was 40 ± 13 years. There were 92 (86.8%) females, 46 (50%) of whom were post-menopausal and 14 (13.2%) males in our cohort with a female-to-male ratio of 6.6:1. The median modified Rodnan skin thickness score was 9. Forty-two (39.6%) patients had at least one comorbidity.

Table 1 summarizes the clinical features of our patients at evaluation.

The autoantibody profile in our cohort has been described in Table 2. We had six patients with positive anti-nuclear antibodies on immunofluorescence with no antibody positivity on the extractable nuclear antigen profile.

Organ involvement and autoantibody correlation:

Table 3 highlights the correlations between disease characteristics and autoantibody profiles of patients in our cohort.

Table 1: Clinical characteristics at evaluation (n = 106)

Clinical features	Number of patients	Proportion (%)
Cutaneous	106	100.0
Diffuse	*62*	*58.5*
Limited	*44*	*41.5*
Raynaud's phenomenon	106	100.0
Arthritis	28	26.4
Myositis	12	11.3
Interstitial Lung Disease	76	71.7
NSIP	*64*	*84.2*
UIP	*12*	*15.7*
Cardiac	15	14.2
PH	28	26.4
Gastrointestinal	85	80.2
Renal	2	1.9
Digital ulcers	72	67.9
Acro-osteolysis	17	16.0
Calcinosis	23	21.7
Telangiectasia	36	34.0
Anaemia	49	46.2

NSIP: Non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia; PH: Pulmonary hypertension.

Table 2: Autoantibody profile of systemic sclerosis patients (n = 106)

Antibody	Number	Proportion (%)
Scl70	65	61.3
CENP	15	14.2
Pm/Scl	7	6.6
Ro 52 (SSA)	11	10.4
Ro 60 (SSA)	9	8.5
La (SSB)	3	2.8
Sm/RNP	15	14.2
RNP68	10	9.4
Ku	3	2.8
PCNA	3	2.8
M2	2	1.9
Nucleosome	2	1.9
sp100	2	1.9
Ribosome-P	1	0.9
dsDNA, Histones, Mi-2, Jo-1, PL-7, PL-12, Gp210, F-Actin, SRP54	0	0

Cutaneous involvement

All of our patients had cutaneous involvement with 58.5% of patients having diffuse and the remaining 41.5% having limited cutaneous involvement. Anti-Scl70 positivity statistically correlated with diffuse cutaneous involvement (OR 3.78, 95% CI 1.66–8.63, p < 0.0001). Similarly, anti-centromere antibodies were significantly associated with the limited cutaneous phenotype (OR 7.38, 95% CI 1.94–28.06, p = 0.001).

Calcinosis was noted on examination in 23 (21.7%) patients and anti-centromere antibodies were significantly associated with them (OR 12, 95% CI 3.53–40.79, p < 0.001). Two patients with concurrent anti-centromere and anti-sp100 autoantibodies had the limited cutaneous phenotype with calcinosis and acro-osteolysis of digits, but without pulmonary or cardiac involvement. Telangiectasias were noted in 34.0%.

Pulmonary involvement

Seventy-six (71.7%) patients had lung involvement in the form of interstitial lung disease (ILD) as reported by

Table 3: Association of autoantibodies with organ involvement

Patient Characteristics n (%)	lcSSc (n = 44)	dcSSc (n = 62)	Scl70 (n = 65)	CENP (n = 15)	Sm/RNP (n = 16)	RNP68 (n = 10)	Pm/Scl (n = 7)
lcSSC (n = 44)	-	-	19 (29.2)	**12 (80)***	8 (50)	5 (50)	3 (42.9)
dcSSc (n = 62)	-	-	**46 (71.8)***	3 (20)	8 (50)	5 (50)	4 (57.1)
Female	40 (91)	52 (83.9)	53 (81.5)	15 (100)	15 (93.8)	9 (90)	7 (100)
Calcinosis	12 (27.3)	11 (17.7)	13 (20)	**10 (66.7)***	1 (6.3)	1 (10)	0 (0)
Acro-osteolysis	10 (22.7)	7 (11.3)	8 (12.3%)	**9 (60)***	1 (6.3)	1 (10)	1 (14.3)
Digital Ulcers	25 (56.8)	**47 (75.8)***	**50 (76.9)***	**6 (40)****	9 (56.3)	6 (60)	3 (42.9)
Telangiectasia	16 (36.4)	20 (32.3)	20 (30.8)	7 (46.7)	6 (37.5)	3 (30)	2 (28.6)
Arthritis	12 (27.3)	25 (40.3)	18 (27.7)	1 (6.7)	**8 (50)***	**6 (60)***	5 (71)
Myositis	4 (9.1)	8 (12.9)	8 (12.3)	0 (0)	3 (18.8)	2 (20)	1 (14.3)
ILD	25 (56.8)	**51 (82.3)***	**58 (89.2)***	**1 (6.7)****	13 (81.3)	7 (70)	7 (100)
Cardiac	12 (27.3)	22 (35.5)	8 (12.3)	3 (20)	1 (6.3)	0 (0)	0 (0)
PH	10 (22.7)	18 (29)	15 (23.1)	5 (33.3)	5 (31.3)	3 (30)	3 (42.9)
GI	30 (68.2)	55 (88.7)	52 (80)	11 (73.3)	11 (68.8)	7 (70)	6 (85.7)
Renal	2 (4.5)	0 (0)	2 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)

Values with *denote positive correlation with $p < 0.05$ and values with ** denote negative correlation with $p < 0.05$. lcSSC: Limited cutaneous systemic sclerosis; dcSSC: Diffuse cutaneous systemic sclerosis; ILD: Interstitial lung disease; PH: Pulmonary hypertension.

a trained radiologist based on high-resolution computed tomography thorax findings with 84.2% showing an non-specific interstitial pneumonia pattern of involvement, while the remaining 15.8% showed the usual interstitial pneumonia pattern. The presence of anti-Scl70 showed a significant association with the presence of ILD (OR 10.59, 95% CI 3.9–28.71, $p < 0.001$) while anti-centromere antibodies were significantly associated with the absence of ILD (OR 0.02, 95% CI 0–0.12, $p < 0.001$).

All 12 patients with concurrent anti-Scl70 and anti-SSA antibodies had a diffuse cutaneous disease and 11 of them had ILD (five with Ro60, four with Ro52 and two with both and all of them had an non-specific interstitial pneumonia pattern on high-resolution computed tomography). However, there was no significantly higher risk of ILD development of this combined positivity when compared with the anti-Scl70 positive group alone.

Sixty-six (62.3%) patients had their pulmonary function testing (PFT) data available at the time of evaluation. Thirty (45.5%) of these patients had normal Forced Vital Capacity (FVC)[9] (≥80%) at evaluation and 18 (60%) of these 30 patients had interstitial lung disease on high-resolution computed tomography findings, out of which only 1 had been labelled as usual interstitial pneumonia, the remaining 17 having non-specific interstitial pneumonia pattern of lung involvement. Eight (12.1%) patients had mild restriction (FVC 70–79%), 24 (36.36%) patients had moderate restriction (FVC 50–69%) and 4 (6.1%) patients had a severe restrictive defect (FVC < 50%). All four patients with severe restriction had diffuse cutaneous involvement and three of them had anti-Scl70 positivity with non-specific interstitial pneumonia on high-resolution computed tomography thorax, while one had Pm/Scl positivity and a usual interstitial pneumonia pattern reported on radiology.

Cardiac involvement

Cardiac involvement was noted in 15 (14.2%) patients with 1 patient having acute myocardial infarct (underwent stenting), 1 patient with non-bacterial thrombotic endocarditis, 2 patients with complete heart block, 2 patients with arrhythmias, 5 patients with mild to moderate pericardial effusion and 4 patients with congestive cardiac failure.

Pulmonary hypertension

Pulmonary hypertension on echocardiography did not correlate with seropositivity of any kind. However, subgroup analysis revealed that the presence of isolated pulmonary hypertension without the presence of interstitial lung disease (pulmonary arterial hypertension) showed a statistically significant association with the presence of anti-centromere antibodies (OR 42, 95% CI 3.03–581.43, $p = 0.01$) and a significant negative association with anti-Scl70 positivity (OR 0.04, 95% CI 0–0.75, $p = 0.01$).

Digital ulceration and acro-osteolysis

Seventy-two (67.9%) patients had digital ulceration in our cohort which was significantly associated with anti-Scl70 positivity (OR 2.88, 95% CI 1.24–6.68, $p = 0.01$). Conversely, the presence of anti-centromere antibodies was negatively associated with the presence of digital ulcers (OR 0.25, 95% CI 0.08–0.78, $p = 0.012$). Diffuse skin involvement was a risk factor for digital ulceration (OR 2.38, 95% CI 1.03–5.48, p 0.04) in our study.

Seventeen (16.0%) patients had autoamputation (acro-osteolysis) of their digits and the presence of anti-centromere positivity was a risk factor for this feature (OR 15.56, 95% CI 4.4–54.99, $P < 0.001$).

Musculoskeletal involvement

Forty (60.6%) patients had musculoskeletal involvement in the form of arthritis or myositis, although none of our patients had met the classification criteria for any autoimmune rheumatic disease other than SSc. Twenty-eight patients (26.4%) had arthritis at evaluation or in the past, while 12 patients (11.3%) had myositis based on elevated CPK levels and muscle weakness. In our cohort, the presence of RNP68 positivity was noted in six (21.4%) patients and this was a statistically significant association (OR 5.04, 95% CI 1.31–19.5, p = 0.01). However, none of these patients had isolated RNP68 positivity, as multiple autoantibodies were overlapping with it in each case. Three patients with limited cutaneous involvement had isolated anti-Ku antibodies and two of these patients also had documented arthritis while the other one had myositis.

Gastrointestinal involvement

Gastrointestinal complaints were the second most common type of features of organ involvement after cutaneous manifestations and were seen in 80.2% of our cohort with all of them presenting with features of gastro-oesophageal reflux disease (GERD), 20 (18.9%) patients having diarrhoea, and 4 (3.7%) patients presenting with dysphagia. There were no significant associations between antibody positivity, cutaneous phenotype and gastrointestinal involvement. We also had 1 single patient with both centromere and anti-M2 antibody and this patient had Primary Biliary Cholangitis overlap.

Other organs and antibodies

Two patients had renal involvement in the form of 2+ proteinuria on 2 separate occasions each on dipstick testing, both of whom were hypertensive at presentation and one of them was on maintenance haemodialysis with a baseline serum creatinine level of 5.6 at evaluation. Both these patients were positive for Scl70 but had limited cutaneous involvement.

Twenty (18.9%) patients had anti-Scl70 concurrently with other antibodies (12 with SSA and 8 patients with Sm/RNP). There were no significant differences in the clinical profiles of patients with isolated anti-Scl70 or anti-Scl70 in conjunction with other autoantibodies.

All 10 (9.4%) patients with RNP68 antibodies had the presence of at least one other autoantibody, of which 8 had Sm/RNP as well. Sp100 antibody was positive in 2 patients and both of them had limited cutaneous disease with Raynaud's phenomenon, calcinosis and acro-osteolysis, as well as having concurrent centromere antibodies.

Discussion

Data from SSc studies have reported variations in the prevalence of disease phenotypes and serologic associations from different geographic and ethnic cohorts.[14] The strength of our study lies in the fact that all of our patients have been tested for the presence of 25 autoantibodies at our specialized immunology laboratory. From our search of the current literature on autoantibody profiles in scleroderma patients, no data is available from a single centre where 25 autoantibodies have been tested in a large cohort. This helped us report minor proportions of patients with relatively rare autoantibodies, although the sample size restricts us from labelling some of these rare autoantibodies as statistically significant. Table 4 compares the cohort characteristics in our study with some of the existing large scleroderma cohorts from multiple geoethnic backgrounds.

We had no patients with coexisting anti-Scl70 and anti-centromere antibodies, similar to most reported populations.[12] The mean age at symptom onset was 40 ± 13 years. Data from a South Indian cohort[10] had explored the possibility of a more severe disease phenotype than Caucasians, especially with a younger age at onset, while Morgan and colleagues reported higher frequencies of younger age at onset and more severe cutaneous and pulmonary disease in African Americans from their GRASP cohort[15] when compared with their EUSTAR counterparts. Diffuse cutaneous involvement (dcSSc) was significantly associated with the presence of interstitial lung disease (ILD), current or past digital ulcers, lower mean BMI values and Scl70 positivity. On the other hand, limited cutaneous disease (lcSSc) was significantly associated with calcinosis and anti-centromere antibodies**.** Nineteen (43%) of the limited cutaneous disease patients had Scl70 antibodies and interstitial lung disease was present in 78.9% of them. Among the diffuse cutaneous involvement patients, 89% of the group with anti-Scl70 antibodies had ILD, as compared to only 62% of the ones without anti-Scl70. This sero-discordance has been described in a study from the Spanish RESCLE cohort in 2018,[16] where the prevalence and severity of ILD were highest in their diffuse cutaneous involvement/anti-Scl70 group as well, while isolated pulmonary hypertension was more in the diffuse cutaneous involvement/anti-centromere group. Calcinosis was seen significantly more in the limited cutaneous disease/anti-centromere group. Interestingly, all seven of our patients who had Pm/Scl antibodies had ILD, but this number was too small for the association to be statistically significant (p = 0.085). The GRASP cohort had shown an association of Pm/Scl antibodies with limited cutaneous disease only.

The prevalence of ILD was more than twice the values reported from the EUSTAR cohort[13] but similar to data from Indian[10] and African American[15] studies. This may be partly explained by a referral bias based on dyspnea or pulmonary findings by a respiratory medicine specialist, while there is a diagnostic delay in patients who may ignore early skin changes. A majority (61.3%) of our patients had anti-Scl70 antibodies which were also significantly associated with the presence of ILD (commonly the non-specific interstitial pneumonia type), lower mean BMI and digital ulcers. Anti-centromere positivity, on the other hand, correlated significantly with calcinosis, the absence of ILD and pulmonary hypertension. We reported a higher prevalence of anti-Scl70 positivity than in Caucasian (36.8%) and African American (30%) studies. In the 66 patients

Table 4: Comparison of cohort characteristics of various ethnicities

Characteristics	Current Study North Indian single centre	EUSTAR Caucasian multicentre[13]	West Indian single centre[10]	South Indian single centre[11]	GRASP African American single centre[15]
Number	106	7655	110	327	1009
Gender (%, M:F)	86.8:13.2	86:14	91:9	88.4:11.6	84:16
Age at Onset (years, mean ± SD)	40 ± 13	42.2 ± 14.9	31.7 ± 9.2	36.3 ± 10.8	39.1 ± 13.7
Symptom Duration (median years, IQR)	6, 3–10	NA	4, 2-8	2.5, 1–5	10, 4–17
BMI (mean ± SD)	24.4 ± 4.5	24.1 ± 4.4	NA	NA	NA
Diffuse vs Limited Cutaneous (%)	58.5 vs 41.5	58.5 vs 37.1	40.9 vs 29.1	94.8 vs 4	57 vs 43
mRSS (median, IQR)	9, 5–14	8, 4–15	NA	16, 8.5–25	14, 5–22
ILD (%)	71.7	51.9	68.2	88.1	68.0
PH (%)	26.4	21.1	47.3	8.1	30.0
Cardiac (%)	14.2	17.4	13.6	4.1	24.0
Renal (%)	1.9	2.1	10.9	0.9	7.0
Myositis (%)	11.3	25.0	39.1 *Musculoskeletal*	12.5	28.0
Arthritis (%)	26.4	15.7	NA	49.5	5.0
Gastrointestinal (%)	80.2	67.3	7.3	49.8	94.0
Calcinosis	21.7	22.1	NA	NA	18.0
Digital Ulcers (%)	67.9	36.0	23.5	56.0	NA
Antibodies (%)					
Scl 70	61.3	36.8	62.7	74.9	30.0
CENP	14.2	32.3	22.7	4.0	8.0
RNAP-3	NA	2.4	NA	NA	13.0
RNP68/U1-RNP/SmRNP	16.0	7.7	NA	7.6	18.0
Pm/Scl	6.6	4.0	NA	NA	6.0
SSA	11.3	NA	NA	NA	17.0

SD: Standard deviation; IQR: Inter-quartile range; BMI: Body mass index; mRSS: Modified Rodnan skin score; ILD: Interstitial lung disease; PH: Pulmonary hypertension.

with PFT data available, 55% had a restrictive defect and 36.4% and 6.1% of these patients had moderate and severe restrictions of FVC, respectively. The EUSTAR cohort reported 32% of patients with FVC restriction and the South Indian study by Janardana *et al*. had 66% of their patients with moderate to severe FVC restriction. Given the greater proportion of diffuse cutaneous disease in our cohort, this prevalence of anti-Scl70 being higher than usual may be partly explained.

Around 26.4% of our patients had pulmonary hypertension and this is slightly less than that reported from Western India (47%) and the GRASP cohorts (30%). We have based our diagnoses on 2D Echocardiography findings, although right heart catheterization (RHC) may be a better modality in this regard. One patient with heart block and one with atrial fibrillation had Ro52 antibodies. Cardiac manifestations were not significantly associated with any of the autoantibodies. We could document renal involvement in the form of proteinuria with hypertension in only two patients which was similar to the EUSTAR data, but much lower than the West Indian[10] or African American[15] cohorts.

Strengths and limitations

The strength of our study is the routine testing for a set of 25 autoantibodies in all our patients, based on which we found 17 patients with RNP68 or Sm/RNP positivity and significant association with current or past synovitis. We also reported three patients with Ku antibodies, all of whom had musculoskeletal features and limited cutaneous disease. These reports of serologic profiles are lacking in most of the existing Indian and international cohorts.

Our study has certain limitations. A single centre may not be enough to capture the true prevalence of disease characteristics in the population. Referral bias has allowed us to collect more patients with diffuse cutaneous disease and anti-Scl70 positivity. To determine clinically meaningful patterns and associations in SSc, we shall need larger samples and data from multiple centres. We were also unable to provide data on RNA-Polymerase antibodies in our study, as the current line immunoassay kit does not provide for it.

Conclusion

Our cohort of North Indian patients had a similar age of onset as their European counterparts, while there was a substantially higher proportion of patients with interstitial lung disease. Two-thirds of our patients were positive for anti-Scl70 antibodies and this was strongly associated with the presence of interstitial lung disease as well as digital ulcers. All patients with anti-Pm/Scl antibodies had interstitial lung disease and antibodies against RNP68 or Sm/RNP were associated with arthritis. Anti-Ku antibodies were rarely reported and these patients had musculoskeletal involvement. The traditional understanding of dividing SSc into limited or diffuse cutaneous phenotypes is now evolving and it may be beneficial to add serologic variables to our diagnostic

workup if we are to predict organ involvement and prognosis of individual patients more accurately.

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Declaration of patient consent

The study has been approved by the Institutional Review Board at Medanta- the Medicity, Gurgaon [MIC 771/2017].

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Conflicts of interest

There are no conflicts of interest.

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