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Racial and Ethnic Disparities in Patients with Systemic Sclerosis: The Brazilian Registry of Systemic Sclerosis (BRASSc) Cohort

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Abstract

Background

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by heterogeneous clinical manifestations and high mortality rates. We aimed to describe the clinical features of the nationwide multicenter Brazilian Registry of Patients with Systemic Sclerosis (BRASSc), including racial and ethnic disparities among participants.

Methods

This is a multicenter observational cohort of patients with SSc from 12 centers in different regions of Brazil. Data of patients included from February 2022 to July 2025 were analysed. Demographics, including self-reported race/ethnicity and clinical, laboratory, serological, and capillaroscopic data were recorded. Comparisons were performed between white and non-white patients.

Results

Among the 471 SSc patients (median age of 56.0 years) included in this cross-sectional analysis, most were white (57.1%) and 42.9% were classified as non-white. Compared with white patients, non-white patients were younger (median 53.0 vs 57.0 years, $p = 0.001$), with a higher frequency of diffuse cutaneous SSc (51.0% vs 25.7%, $p < 0.001$) and interstitial lung disease (ILD) (63.4% vs 55.7%, $p = 0.014$). Multivariate analysis revealed that non-white race/ethnicity was significantly associated with low forced vital capacity values ($\beta = -5.11\%$, 95% CI -9.94 to -0.27, $p = 0.038$), high skin scores ($\beta = +2.66$, 95% CI 0.95–4.38, $p = 0.002$), and high disease severity scores ($\beta = +0.75$, 95% CI 0.20–1.30, $p = 0.007$). Phenotype cluster analysis revealed three different clusters: diffuse, limited, and ILD phenotypes. Non-white patients were more frequent in the diffuse phenotype, comprising 58.8% of patients.

Conclusions

Significant racial and ethnic disparities were observed among Brazilian patients with SSc, including more extensive disease, greater pulmonary involvement, and greater functional impact. These findings suggest the need for a more vigilant approach among minority groups.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune rheumatic disease characterized by immune dysregulation of both the innate and adaptive immune systems, vascular abnormalities, and progressive fibrosis of the skin and multiple internal organs, including the heart, lungs, kidneys, and gastrointestinal

tract [1]. Despite some advances, compared with other rheumatic diseases, SSc is associated with higher mortality rates [2–4].

SSc is a rare and heterogeneous disease with highly variable clinical presentation, organ involvement, and an unpredictable clinical course [2]. Patients with SSc are usually classified into three major clinical subtypes on the basis of the extent of skin involvement: diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), and SSc sine scleroderma. Patients with dcSSc exhibit a widespread skin thickening localized proximal to the elbows or knees and have a higher risk of visceral involvement and a higher mortality rate, whereas in patients with lcSSc, skin thickening is limited to the distal extremities, with or without facial involvement [1]. Patients without skin fibrosis, despite the presence of characteristic visceral manifestations of SSc, are considered to have SSc sine scleroderma [5, 6]. In all subsets, patients can experience visceral involvement [7]. Finally, patients might also be classified as having “early” or “very early” SSc [8, 9]. However, because of the heterogeneity of SSc, many crucial aspects of disease progression and severity are not captured by skin-based classification alone [10].

Clinical manifestations, and disease severity can vary according to race, geographical factors, and genetic factors [11–14]. For example, different HLA haplotypes were associated with distinct disease subtypes in African and European Americans [13]. In this context, national SSc registries are important for providing large and homogeneous patient characterization, as well as for a better understanding of the expression of the disease in different geographical regions and among populations of different ethnicities [15]. Additionally, registries are important for identifying factors associated with disease morbidity and mortality in a real-life scenario [15]. Several registries have been published describing the clinical characteristics of SSc in Europe and North America [15–19]. Nonetheless, data evaluating SSc patients from South America are scarce and are mostly derived from a single center [20]. Brazil is a continental country with highly racial miscegenation, which underscores the importance of evaluating the epidemiological and clinical features of SSc in Brazilian patients.

The present study is a cross-sectional analysis of the nationwide multicenter Brazilian Registry of Patients with Systemic Sclerosis (BRASSc) from the Brazilian Society of Rheumatology. First, we aimed to describe the clinical features of a large cohort of Brazilian patients with SSc. Second, differences between white and non-white patients were evaluated. Finally, three patient clusters for disease severity were proposed based on clinical relevance and internal validation metrics: ILD phenotype, limited phenotype, and diffuse phenotype.

Methods

Patients and study design

The BRASSc is a multicenter, observational, prospective cohort that enrols patients with SSc from centers in different regions of Brazil. Twelve centers with experience in the follow-up and management

of SSc participated in patient recruitment. The first patient was enrolled in February 2022, and data registered up to July 2025 were analysed.

The inclusion criteria were ≥ 18 years of age and a clinical diagnosis of SSc by an expert rheumatologist. Patients were excluded if they had a diagnosis of any other autoimmune rheumatic disease, including rheumatoid arthritis, systemic lupus erythematosus, or inflammatory myopathies.

Demographic, clinical, laboratory, serological, and capillaroscopic data were recorded in accordance with a standard protocol. Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure web-based platform for construction and data storage (website: https://www.redcapbrasil.com.br/).

Assessment

Sociodemographic variables and SSc characteristics, including age, sex, and race/ethnicity according to the *Instituto Brasileiro de Geografia e Estatística* (IBGE) [self-reported skin colour, including white, black, mixed (*pardo*), yellow (Asian Brazilians), and indigenous] [21] were collected at inclusion through interviews, physical examinations and medical chart revision.

Clinical data, including the duration of Raynaud's phenomenon, disease duration (defined as the time between the first non-Raynaud symptom and the inclusion visit), disease subtype, fulfilment of the 2013 ACR/EULAR classification criteria for SSc [22], and clinical manifestations, were recorded in accordance with a standard protocol.

The SSc patients were classified into diffuse cutaneous (skin thickening extended proximally to the elbows and knees with or without truncal involvement), limited cutaneous SSc (skin thickening restricted distally to the elbows and knees, with or without facial involvement), and sine scleroderma (no skin thickening and one or more of the typical types of visceral involvement in SSc) [6, 23]. Patients with early SSc were classified according to the LeRoy and Medsger criteria from 2001 [8].

In addition, the following clinical manifestations (present at inclusion or previously) were evaluated: Raynaud's phenomenon, digital ulcers, telangiectasias, calcinosis, tendon friction rubs, arthritis (inflammatory changes observed in more than 2 joints), myositis (muscle weakness and/or elevated serum creatine kinase), oesophageal involvement, arrhythmias, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), and scleroderma renal crisis (new onset of significant hypertension and rapid deterioration of renal function and/or typical histopathological abnormalities on renal biopsy) [24]. ILD was defined as the presence of interstitial abnormalities on high-resolution chest computed tomography (CT). PAH was confirmed by right heart catheterization (RHC) as previously defined [25]. Pulmonary function tests, including diffusing lung capacity for carbon monoxide (DLCO) and forced vital capacity (FVC), were also performed. For all the data, only those tests performed during the last 12 months of the evaluation were considered. The modified Rodnan skin score (mRSS) [26] was performed in all subjects.

For antibody testing using the indirect immunofluorescence assay (IFA) in Hep-2 cells, serum samples displaying a characteristic IFA pattern at a ≥ 1/80 dilution were considered positive. We also collected data on the presence of anticentromere (ACA), anti-topoisomerase I (anti-topo I), and anti-RNA polymerase III antibodies, as well as erythrocyte sedimentation rate (ESR) values and creatine phosphokinase (CPK) levels.

Nailfold capillaroscopy (NFC) was performed using a stereomicroscope at 10–25x magnification or videocapillaroscopy (200x magnification) as previously described [27, 28]. The following parameters were recorded: the number of capillaries per millimetre in the eight fingers (excluding thumbs) and the presence of a scleroderma pattern [27, 28].

Disease severity was also assessed using the Scleroderma Health Assessment Questionnaire (sHAQ) [29] and the Medsger Disease Severity Scale [30].

Ethics

The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Ethical Committee of the Federal University of São Paulo (n. 0407/2021; CAAE:45565621.4.1001.5505). In addition, local ethics committee approval was obtained from all the participating centers. Written informed consent was obtained from all participants.

Statistical analysis

For statistical analysis, patients were grouped into two groups: white and non-white. The data are presented as the means and standard deviations (SDs), or medians and interquartile ranges (IQRs), and frequencies. Normality was assessed by the Shapiro–Wilk and Kolmogorov–Smirnov tests. Continuous variables were compared using the t-test or the Mann–Whitney U test. Categorical variables were analysed using the chi-square test or Fisher's exact test. Correlations between clinical variables were assessed using the Spearman correlation test.

To determine whether race/ethnicity independently predicted different disease profiles, we performed univariate and multivariate logistic regression analyses for five distinct outcomes: ILD, mRSS, FVC%, total Medsger score, and Medsger score, excluding lung involvement. Each independent variable was tested individually in relation to the outcome of interest, with the aim of initial screening for multivariate modelling. Univariate logistic or linear regression was performed for binary and continuous outcomes. Candidate variables for the multivariate models were selected based on prespecified criteria, with a p-value ≤ 0.10 in the univariate analyses and/or recognised clinical relevance in the literature (e.g., specific autoantibodies and classic organic manifestations of SSc). Multivariate logistic regression and linear regression models were constructed by simultaneously including the selected variables. The empirical rule of at least 10 events per variable was applied in the logistic models to minimize overfitting. Variables with strong conceptual or clinical correlations were assessed for redundancy, avoiding implicit

collinearity. The results were presented as odds ratios (ORs) or β coefficients, with 95% confidence intervals (CIs) and p values.

Finally, unsupervised cluster analysis was performed to identify distinct clinical phenotypes. The clusters obtained were subsequently compared regarding clinical, laboratory, and outcome characteristics, using appropriate tests for each type of variable.

For all analyses, a p-value < 0.05 was considered statistically significant. Analyses were performed using the statistical software Jamovi, version 2.7 (2025).

Results

Study population and clinical characteristics

A total of 471 patients with SSc were included: 48% from the southwest region, 34% from the south region, 15% from the central-west region, and 3% from the northeast region of Brazil. The patients were predominantly females (91.9%), with a median age of 56.0 years (IQR 46–64). Regarding race/ethnicity, 269 patients (57.1%) were classified as white and 202 (42.9%) as non-white. Among non-white patients, 61 (13.0%) were black, 139 (29.5%) were mixed, and 2 (0.4%) were indigenous. No patient was classified as yellow (Table 1).

Table 1
Demographic and Clinical Characteristics of the 471 Systemic Sclerosis Patients by Ethnicity

Variable	Total (n = 471)	White (n = 269)	Non-White (n = 202)	p-value
Age, median (IQR)	56.0 (46.0–64.0)	57.0 (48.0–67.0)	53.0 (43.0–62.0)	0.001
Female sex	433 (91.9%)	250 (92.9%)	183 (90.6%)	0.364
Duration of RP, median (IQR) (years)	12.0 (7.0–21.0)	14.0 (7.0-21.5)	11.0 (6.0–20.0)	0.682
Disease duration, median (IQR) (years)	11.0 (6.0–17.0)	11.0 (6.0–17.0)	10.0 (6.0–17.0)	0.412
Clinical Subset				
. Limited cutaneous	260 (55.2%)	174 (64.7%)	86 (42.6%)	< 0.001
Diffuse cutaneous	172 (36.5%)	69 (25.7%)	103 (51.0%)	< 0.001
Sine scleroderma	38 (8.1%)	25 (9.3%)	13 (6.4%)	0.261
Early SSc	1 (0.2%)	1 (0.2%)	0 (0%)	—
mRSS, median (IQR)	6 (2–12)	5 (1–10)	9 (3–15)	< 0.001
RP	465 (98.7%)	267 (99.3%)	198 (98.0%)	0.442
Digital ulcers	244 (51.8%)	114 (42.4%)	130 (64.4%)	< 0.001
Oesophageal involvement	426 (90.4%)	242 (91.0%)	184 (91.1%)	0.576
Telangiectasias	347 (73.7%)	205 (77.1%)	142 (70.3%)	0.261
Tendon friction rubs	53 (11.3%)	26 (10.2%)	27 (13.4%)	0.202
Arthritis	254 (53.9%)	125 (46.5%)	129 (63.9%)	< 0.001
Myositis	79 (16.8%)	35 (13.0%)	44 (21.8%)	0.008
Arrhythmia	178 (37.8%)	97 (36.1%)	81 (40.1%)	0.376
Calcinosis	59 (12.5%)	38 (14.1%)	21 (10.4%)	0.329
Renal crisis	14 (3.0%)	6 (2.2%)	8 (4.0%)	0.273
ILD	269 (57.1%)	141 (55.7%)	128 (63.4%)	0.014

Data are presented as median (IQR), mean ± SD, or n (%).

Abbreviations: ANA: antinuclear antibody; DLCO: diffusing capacity; FVC: forced vital capacity; IQR: interquartile range; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; RP: Raynaud's phenomenon; SD: scleroderma; SHAQ: Scleroderma Health Assessment Questionnaire; SSc: systemic sclerosis.

Variable	Total (n = 471)	White (n = 269)	Non-White (n = 202)	p-value
FVC %, median (IQR)	80.0 (64–95)	83.0 (70–96)	73.0 (58–88)	< 0.001
DLCO %, median (IQR)	72.0 (55–90)	78.5 (60–95)	63.0 (45–80)	0.001
Pulmonary hypertension	25 (5.3%)	14 (5.2%)	11 (5.4%)	1.000
ANA positive	440 (93.4%)	259 (96.3%)	181 (89.6%)	0.007
Anti-centromere	124 (26.3%)	90 (33.5%)	34 (16.8%)	< 0.001
Anti-topo I (n = 399)	113 (28.3%)	55 (23.6%)	58 (34.9%)	0.018
Anti-RNA pol III (n = 121)	17 (14.0%)	9 (13.0%)	8 (15.4%)	0.582
Medsger score, median (IQR)	5.0 (3–7)	5.0 (3–6)	6.0 (4–8)	< 0.001
SHAQ score, median (IQR)	0.7 (0.3–1.3)	0.6 (0.2–1.1)	0.8 (0.4–1.4)	0.001
SD pattern (n = 282)	248 (87.9%)	141 (87.6%)	107 (88.4%)	0.721
Capillary density, mean ± SD	7.1 ± 1.7	7.1 ± 1.7	7.0 ± 1.7	0.520
Data are presented as median (IQR), mean ± SD, or n (%).				
Abbreviations: ANA: antinuclear antibody; DLCO: diffusing capacity; FVC: forced vital capacity; IQR: interquartile range; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; RP: Raynaud's phenomenon; SD: scleroderma; SHAQ: Scleroderma Health Assessment Questionnaire; SSc: systemic sclerosis.				

Compared with white patients, non-white patients were younger (median 53.0 vs 57.0 years, p = 0.001), and dcSSc was significantly more prevalent among non-white patients (51.0% vs 25.7%, p < 0.001). Moreover, the mRSS was significantly higher in non-white patients than in white patients (median 9.0 vs 5.0, p < 0.001), and the frequency of digital ulcers (64.4% vs 42.4%, p < 0.001), arthritis (63.9% vs 46.5%, p < 0.001), and myositis (23.3% vs 13.4%, p = 0.008) was significantly more prevalent in non-white patients than in white patients. ILD was present in 57.1% of the cohort and was also significantly more frequent among non-white patients (63.4% vs 55.7%, p = 0.014). Pulmonary function parameters demonstrated clinically meaningful differences between groups. Compared with white patients, non-white patients had lower FVC values (median 73.0% vs 83.0%, p < 0.001) and lower DLCO (median 63.0% vs 78.5%, p = 0.001) (Table 1).

The autoantibody profile differed significantly between the two groups (Table 1). Anti-topoisomerase I antibodies were more frequent in non-white patients than in white patients (34.9% vs 23.6%, p = 0.018). Conversely, ACA positivity was significantly lower in non-white participants than in white participants (16.8% vs 33.5%, p < 0.001). Moreover, compared with white patients, non-white patients had significantly higher ESR values (median 27.5 vs. 19.0 mm/h, p = 0.001) and CPK levels (median 125 vs. 105 U/L, p = 0.020). The Medsger severity score was significantly higher in non-white patients than in white patients

(median 6.0 vs 5.0, p < 0.001), as was the SHAQ score (median 0.8 vs 0.6, p = 0.001), indicating greater functional impairment in non-white patients. Nailfold capillaroscopy revealed an SD pattern in 87.6% white patients and 88.4% non-white patients (Table 1).

Univariate and multivariate regression analyses

Univariate analysis revealed that ILD was significantly associated with non-white ethnicity (OR 1.62, 95% CI 1.10–2.41, p = 0.016), anti-topoisomerase I (OR 8.03, 95% CI 4.21–15.32, p < 0.001), and dcSSc (OR 4.54, 95% CI 2.85–7.24, p < 0.001). ACA was protective against the presence of ILD (OR 0.12, 95% CI 0.07–0.20, p < 0.001). In the multivariate model adjusted for age, sex, clinical subset, and autoantibody status, anti-topoisomerase I remained the strongest predictor of ILD (OR 5.76, 95% CI 2.45–13.55, p < 0.001), whereas ACA remained protective (OR 0.14, 95% CI 0.08–0.27, p < 0.001) (Table 2 and Supplemental Material).

Table 2
Multivariate Analysis of Predictors for Clinical Outcomes in Systemic Sclerosis

	OR/β	95% CI	P
ILD			
Anti-Topoisomerase I	5.76	2.45–13.55	< 0.001
Anti-Centromere	0.14	0.08–0.27	< 0.001
Diffuse Cutaneous SSc	1.78	0.93–3.39	0.081
Non-White Race/Ethnicity	1.26	0.72–2.19	0.422
Age (per year)	1.04	1.02–1.06	< 0.001
Female Sex	0.79	0.27–2.26	0.657
FVC %			
Anti-Centromere	+ 11.43	5.92 to 16.94	< 0.001
Diffuse Cutaneous SSc	-11.07	-16.77 to -5.38	< 0.001
Non-White Race/Ethnicity	-5.11	-9.94 to -0.27	0.038
Female Sex	+ 6.32	-1.87 to 14.51	0.130
Anti-Topoisomerase I	-1.22	-7.02 to 4.58	0.679
Age (per year)	-0.08	-0.25 to 0.09	0.336
mRSS			
Anti-Topoisomerase I	+ 6.98	5.01 to 8.95	< 0.001
Non-White Race/Ethnicity	+ 2.66	0.95 to 4.38	0.002
Age (per year)	-0.09	-0.15 to -0.03	0.005
Anti-Centromere	+ 0.10	-1.86 to 2.06	0.923
Female Sex	-2.58	-5.71 to 0.54	0.105
Total Medsger Score			
Diffuse Cutaneous SSc	+ 1.94	1.29 to 2.58	< 0.001
Anti-Topoisomerase I	+ 1.28	0.61 to 1.96	< 0.001
Non-White Race/Ethnicity	+ 0.75	0.20 to 1.30	0.007
Anti-Centromere	-0.11	-0.74 to 0.52	0.727

Abbreviations: CI: confidence interval; FVC: forced vital capacity; mRSS: modified Rodnan skin score; OR: Odds Ratio; SSc: systemic sclerosis;; β = Beta coefficient;.

	OR/β	95% CI	P
ILD			
Age (per year)	+ 0.01	-0.01 to 0.03	0.153
Female Sex	+ 0.11	-0.87 to 1.09	0.829
Medsger Score without Lung			
Diffuse Cutaneous SSc	+ 1.78	1.20 to 2.37	< 0.001
Anti-Topoisomerase I	+ 1.05	0.44 to 1.66	< 0.001
Non-White Race/Ethnicity	+ 0.54	0.05 to 1.04	0.031
Anti-Centromere	+ 0.53	-0.04 to 1.10	0.069
Age (per year)	+ 0.00	-0.02 to 0.02	0.774
Female Sex	+ 0.22	-0.66 to 1.10	0.625
Abbreviations: CI: confidence interval; FVC: forced vital capacity; mRSS: modified Rodnan skin score; OR: Odds Ratio; SSc: systemic sclerosis;; β = Beta coefficient;.			

Note: All models adjusted for age, sex, race/ethnicity, disease subtype, and autoantibody status. Sample sizes: ILD (N=343), mRSS (N=345), FVC% (N=298), Medsger scores (N=354). Diffuse SSc excluded from mRSS model due to multicollinearity (ρ=0.50).

Moreover, in the multivariate model, non-white race/ethnicity was significantly associated with lower FVC values (β = −5.11%, 95% CI − 9.94 to − 0.27, p = 0.038), representing a clinically meaningful 5.11 percentage-point reduction in FVC compared with white patients. DcSSc was associated with an 11.07% reduction in FVC (β = −11.07, 95% CI − 16.77 to − 5.38, p < 0.001), while ACA positivity was protective (β = +11.43, 95% CI 5.92–16.94, p < 0.001) (Table 2).

In the multivariate model, non-white race/ethnicity was independently associated with higher mRSS values (β = +2.66, 95% CI 0.95–4.38, p = 0.002), indicating that non-white patients had, on average, 2.66 points higher skin scores after the adjustment for autoantibody status, age, and sex. Anti-topoisomerase I was the strongest predictor (β = +6.98, 95% CI 5.01–8.95, p < 0.001), whereas younger age was associated with more extensive skin involvement (β = −0.09 per year, 95% CI − 0.15 to − 0.03, p = 0.005) (Table 2).

Non-white race/ethnicity was also significantly associated with increased disease severity evaluated with the total Medsger score (β = +0.75, 95% CI 0.20–1.30, p = 0.007). DcSSc (β = +1.94, 95% CI 1.29–2.58, p < 0.001) and anti-topoisomerase I (β = +1.28, 95% CI 0.61–1.96, p < 0.001) were also significant independent predictors (Table 2).

To determine whether the effect of ethnicity on disease severity was driven primarily by pulmonary involvement, we performed an additional analysis using the Medsger score excluding the lung component. Non-white ethnicity remained a significant independent predictor (β = +0.54, 95% CI 0.05–1.04, p = 0.031), demonstrating that the association with disease severity extends beyond pulmonary manifestations to affect multiple organ systems (Table 2).

Cluster analysis of disease phenotypes

To identify distinct disease phenotypes and explore their relationships with race/ethnicity, K-means clustering was performed on 281 patients with complete data for key clinical variables. Three clusters were identified based on clinical relevance and internal validation metrics (Silhouette coefficient = 0.244) (Table 3, Fig. 1).

Table 3
Characteristics of Disease Phenotype Clusters in Systemic Sclerosis

Characteristic	Cluster 1: ILD	Cluster 2: Limited	Cluster 3: Diffuse	p-value
N (%)	115 (40.9%)	98 (34.9%)	68 (24.2%)	
Age, mean ± SD	55.9 ± 12.1	56.6 ± 14.2	49.6 ± 13.5	< 0.001
Diffuse form (%)	31.3%	2.0%	98.5%	< 0.001
Anti-topoisomerase I (%)	19.1%	3.1%	79.4%	< 0.001
Anti-centromere (%)	8.7%	73.5%	2.9%	< 0.001
mRSS, mean	5.4	4.9	18.3	< 0.001
FVC (%), mean	70.7%	95.1%	67.8%	< 0.001
Medsger score, mean	5.3	3.9	8.5	< 0.001
ILD present (%)	92.2%	7.1%	85.3%	< 0.001
Non-White ethnicity (%)	38.3%	23.5%	58.8%	< 0.001
K-means clustering (K = 3) performed on 281 patients with complete data. Silhouette coefficient = 0.244.				
Abbreviations: FVC: forced vital capacity; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; SD: standard deviation.				

Cluster 1 (ILD phenotype; n = 115, 40.9%) was characterized by predominant pulmonary involvement (92.2% with ILD) despite relatively mild skin disease (mean mRSS 5.4). This cluster showed an intermediate presence of anti-topoisomerase I (19.1%) and intermediate severity scores (mean Medsger 5.3).

Cluster 2 (limited phenotype; n = 98, 34.9%) represented classic limited cutaneous SSc, characterized by a high frequency of ACA positivity (73.5%), preserved lung function (mean FVC 95.1%), a low frequency

of ILD (7.1%), and the lowest disease severity scores (mean Medsger 3.9).

Cluster 3 (diffuse phenotype; n = 68, 24.2%) represented the most severe disease phenotype, characterized by near-universal diffuse skin involvement (98.5%), a high frequency of anti-topo I (79.4%) and ILD (85.3%), extensive skin disease (mean mRSS 18.3), and the highest Medsger severity score (mean score of 8.5). Patients in this cluster were significantly younger. Importantly, non-white ethnicity was significantly overrepresented in Cluster 3, comprising 58.8% of the patients, compared with 38.3% in Cluster 1 and only 23.5% in Cluster 2 ($p < 0.001$) **(**Fig. 1C**)**.

Discussion

In the present study, we evaluated a large cohort of SSc patients from different centers in Brazil. Interestingly, our findings confirm that race and ethnicity have a strong impact on clinical presentation and disease severity. Non-white SSc patients, including black, mixed, and indigenous patients, had more severe disease, characterized by a higher frequency of ILD, worse FVC and DLCO, more severe skin involvement, and higher Medsger disease severity scores. Interestingly, the clustering approach revealed three different phenotypes: diffuse, limited, and ILD phenotypes. Importantly, patients in the diffuse phenotype, characterized by more severe disease, were predominantly non-white.

Compared with white patients, non-white patients in our cohort were younger at evaluation and had a similar disease duration, suggesting an intrinsically more aggressive disease course rather than delayed diagnosis or longer disease evolution. These findings are similar to those reported in other SSc cohorts [11, 31]. In a study from the Johns Hopkins Scleroderma Center, African American patients were younger than white patients, developed severe organ involvement earlier, and had worse survival despite a comparable disease duration [11]. Recently, in 2025, Tukpah et al. reported similar results in a cohort of 756 SSc patients, in which Black/African American and Hispanic patients were significantly younger than white patients [31]. The racial and ethnic disparities among SSc patients suggest the need for careful and vigilant evaluation, especially among younger individuals.

Moreover, compared with white patients, non-white patients had a significantly higher mRSS, a higher frequency of dcSSc, and higher serum inflammatory markers. These findings are in agreement with those of previous studies from Native North American, Hispanic, and East Asian cohorts reporting higher disease severity, diffuse cutaneous involvement, and worse outcomes among those patients [11, 16, 32–34].

Unlike most previous studies derived from relatively homogeneous populations, our data originate from a highly mixed South American population with distinct genetic backgrounds and socioeconomic features. To the best of our knowledge, only one monocentric study evaluated racial differences in 260 SSc patients from Brazil [35]. Confirming our results, “African-Brazilians” had overall more severe disease than white patients. Our findings reinforce the concept that ethnic disparities in SSc severity are a reproducible and clinically relevant phenomenon across different geographic regions.

Some studies have suggested that genetic background plays a relevant role in SSc susceptibility. Epigenetic mechanisms, especially DNA methylation patterns, may also influence disease severity and mortality. Certain genetic markers are more prevalent among African American populations, while some studies have suggested higher levels of gene hypermethylation in individuals of European ancestry, which may contribute to differences in inflammatory responses [36].

In addition to race and ethnicity, anti-topo I was also associated with the presence of ILD, higher mRSS values, and higher disease severity scores in multivariate analysis. In particular, the presence of ILD was largely mediated by the autoantibody profile. Indeed, after the adjustment for anti-topo I and ACA antibodies, ethnicity was no longer independently associated with ILD, while anti-topo I remained the strongest predictor factor. These findings are consistent with those of previous studies showing that autoantibodies are strong determinants of disease phenotype and prognosis across different ancestral backgrounds [12, 13, 32]. On the other hand, a recent study evaluating electronic health records from Brigham, USA, revealed increased odds of ILD for Asian and Black/African American patients, even after adjusting for sociodemographic covariates, but not for anti-topo I [31]. Similarly, in a large study evaluating the association between race, autoantibodies, and disease outcomes in SSc patients, autoantibodies were associated with specific manifestations of the disease, including ILD, but did not fully account for racial differences in the severity of SSc [34]. Taken together, these findings indicate that other factors may influence racial and ethnic disparities among SSc patients. Indeed, previous studies have suggested that access to care and other socioeconomic factors may also influence disease outcomes among SSc patients [37].

Our sample was predominantly composed of patients enrolled in the Unified Health System (SUS), an entity in Brazil that guarantees universal and free access to medications and procedures for the patients, theoretically eliminating direct financial barriers to treatment. This context distinguishes our cohort from North American studies, in which ethnic disparities in SSc severity are frequently attributed to differences in access to health insurance or the availability of specialized centers. This difference reinforces the importance of genetic background as an important factor involved in the severity of SSc. However, patients from minority ethnic groups frequently have lower levels of education and income, worse housing conditions, and greater occupational exposure to pollution and passive smoking. Moreover, practical barriers, such as difficulties attending appointments and a limited understanding of the chronic nature of the disease, can hinder adherence to treatment. These factors could contribute to greater disease severity or a lower therapeutic response, even when treatment is offered equitably. The finding that ethnic disparities persist even in a universal healthcare system suggests that guaranteeing access, while necessary, is not sufficient to eliminate health inequities. Thus, further research is needed to better understand the factors that contribute to the disparities between these groups [34].

In our study, despite the loss of an independent association between ethnicity and ILD, non-white ethnicity remained independently associated with worse pulmonary function, even after the adjustment for ILD, disease subset, and autoantibody status. Similar dissociations between the presence of ILD and

lung function decline have been reported in the EUSTAR and UK cohorts, suggesting that factors such as the extent and severity of fibrosis may contribute to functional impairment [31].

Ethnicity remained independently associated with higher global disease severity, even after the exclusion of pulmonary involvement from the Medsger score. These findings indicate that the observed disparities extend across multiple organ systems, which is consistent with previous observations showing that overall disease burden, rather than single-organ involvement, drives disease severity in SSc [32–35].

SSc is a complex disease that affects multiple organs. Thus, more recently, skin-based classification alone has not been considered sufficient for subtyping these patients [10]. Using unsupervised clustering, we identified three clinically meaningful disease phenotypes: ILD, limited, and diffuse SSc. The diffuse phenotype was associated with clinical characteristics of more severe disease, including diffuse skin involvement and a higher mRSS, a high frequency of anti-topo I and ILD, and higher Medsger scores. Notably, non-white patients were significantly more prevalent in this cluster, confirming a more severe disease phenotype in these patients.

Our study has several limitations, including a lack of information about education and income. Moreover, the cross-sectional analyses limit causal inference and longitudinal outcome assessment. Nevertheless, the BRASSc registry provides a robust platform for future longitudinal analyses evaluating disease progression, survival, and treatment response, similar to established international registries such as EUSTAR [38] and SPRING [18].

Conclusion

Non-white ethnicity in this multiracial/ethnic cohort is not merely a demographic variable, but also a marker of a severe phenotype. Non-white patients presented with more extensive disease, greater pulmonary involvement, and greater functional impact. These findings corroborate the notion that race is related to a distinct phenotypic profile in scleroderma and could justify a more rigorous initial assessment and close follow-up among minority groups.

Abbreviations

ACA
anti-centromere antibody
ANA
antinuclear antibody
Anti-topo I
Anti-topoisomerase I
BRASSc
Brazilian Registry of Patients with Systemic Sclerosis
CI
confidence interval

dcSSc
diffuse cutaneous SSc
DLCO
diffusing capacity
FVC
forced vital capacity
IQR
interquartile range
ILD
interstitial lung disease
lcSSc
limited cutaneous SSc
mRSS
modified Rodnan skin score
OR
Odds Ratio
RP
Raynaud's phenomenon
SD
scleroderma
SHAQ
Scleroderma Health Assessment Questionnaire
SSc
systemic sclerosis
β
Beta coefficient

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Ethical Committee of the Federal University of São Paulo (n. 0407/2021; CAAE:45565621.4.1001.5505). Written informed consent was obtained from all participants.

Consent for publication: not applicable

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available on a reasonable request to the corresponding author.

Competing interests

The authors declare no conflicts of interest.

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Author's contributions

All authors made a substantial contribution to discussion of the content and reviewed/edited the manuscript before submission. C.K. and F.G. performed the statistical analysis and wrote the manuscript.

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Figures

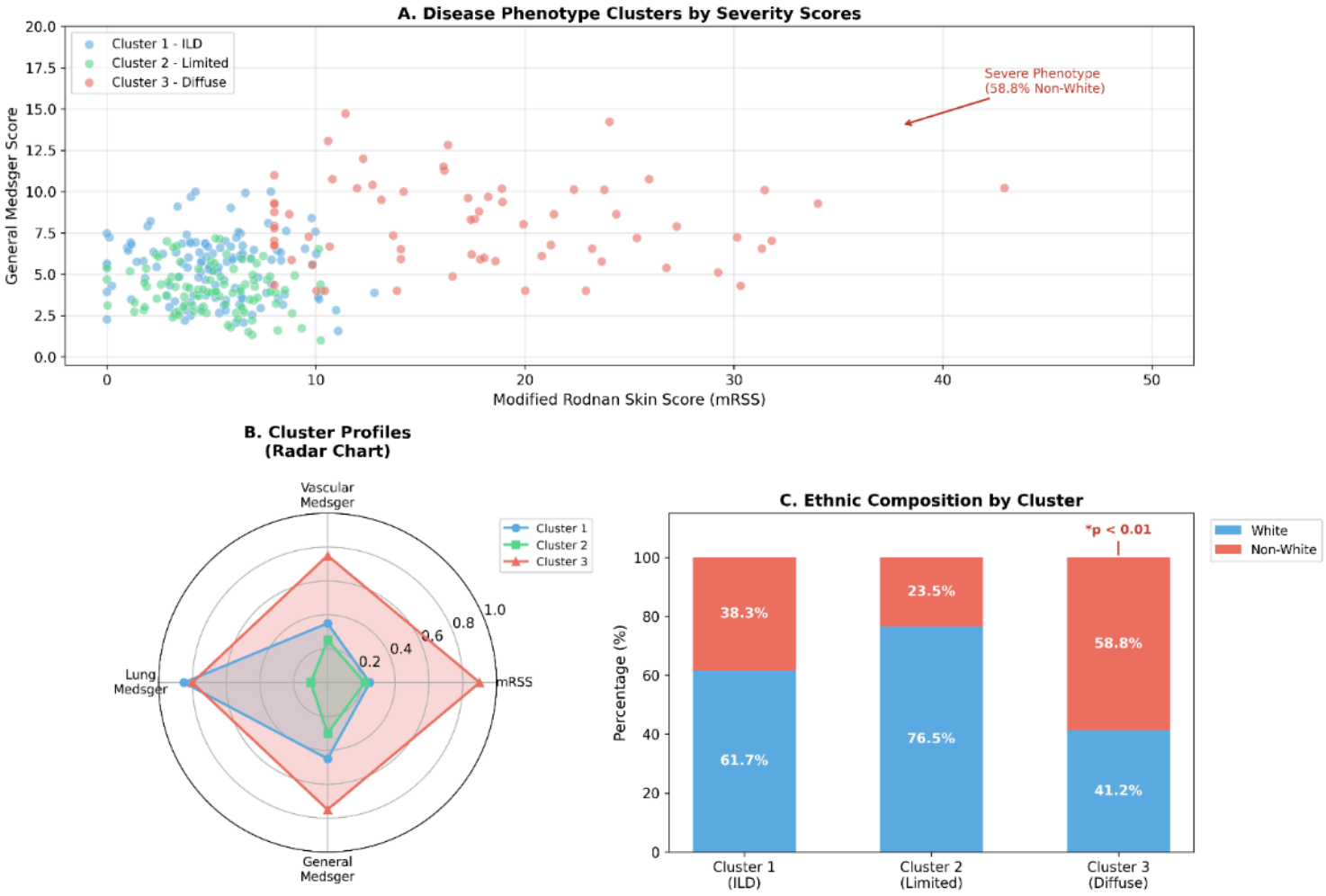


Figure 1

Disease Phenotype Clustering Analysis

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