Clinical Rheumatology (2020) 39:9–17
https://doi.org/10.1007/s10067-019-04575-5

ORIGINAL ARTICLE

Clinical and laboratory features of African-Brazilian patients with systemic sclerosis

Cristiane Mendes[1,2] · Vilma S. T. Viana[1] · Sandra G. Pasoto[1] · Elaine P. Leon[1] · Eloisa Bonfa[1] · Percival D. Sampaio-Barros[1,3]

Received: 5 January 2019 / Revised: 15 April 2019 / Accepted: 22 April 2019 / Published online: 7 May 2019

Abstract

Objective African-Brazilians comprise a group of blacks and "pardos." As racial differences can be associated with distinct presentations, we evaluated the clinical and serological associations of African-Brazilians with systemic sclerosis (SSc).

Methods Sera from 260 adult SSc patients (203 whites and 57 African-Brazilians) were evaluated. Patients with overlap syndromes were excluded. Clinical and demographic data were obtained from an electronic register database. Laboratory analysis included the following: anti-CENP-A/CENP-B, Scl70, RNA polymerase III, Ku, fibrillarin, Th/To, PM-Scl75, and PM-Scl100 by line immunoassay and anti-nuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cells.

Results African-Brazilian SSc patients presented shorter disease duration (12.8 ± 6.5 vs. 15.9 ± 8.1 years, $p = 0.009$), higher frequency of nucleolar ANA pattern (28% vs. 13%, $p = 0.008$), and lower frequencies of centromeric ANA pattern (14% vs. 29%, $p = 0.026$) and CENP-B (18% vs. 34%, $p = 0.017$), as well as an association with severe interstitial lung disease (58% vs. 43%; $p = 0.044$). Further comparison of ethnic groups according to subsets revealed that diffuse SSc African-Brazilian patients presented higher frequency of pulmonary hypertension ($p = 0.017$), heart involvement ($p = 0.037$), nucleolar ANA pattern ($p = 0.036$), anti-fibrillarin antibodies ($p = 0.037$), and higher mortality (48% vs. 19%; $p = 0.009$). A different pattern was observed for the limited subset with solely a lower frequency of esophageal involvement ($p = 0.050$) and centromeric ANA pattern ($p = 0.049$). Survival analysis showed that African-Brazilians had a higher mortality, when adjusted for age, gender, and clinical subset (RR 2.06, CI 95% 1.10–3.83, $p = 0.023$).

Conclusion African-Brazilians have distinct characteristics according to clinical subset and an overall more severe SSc than whites, similar to the blacks from other countries.

Key Points

- *African-Brazilian SSc patients were associated with severe interstitial lung disease and nucleolar ANA pattern when compared to white SSc patients.*
- *When disease subsets were considered, African-Brazilian patients with diffuse SSc presented association with pulmonary hypertension, heart involvement, nucleolar ANA pattern, and anti-fibrillarin antibodies.*
- *White SSc patients were associated with centromeric ANA pattern.*
- *Survival analysis at 5, 10, 15, and 20 years, adjusted for age, gender, and disease subset, was significantly worse in African-Brazilian SSc patients.*

Keywords African-Brazilians · Autoantibodies · Diffuse scleroderma · Ethnicity · Limited scleroderma · Systemic sclerosis

✉ Percival D. Sampaio-Barros
pdsampaiobarros@uol.com.br

Cristiane Mendes
cmsreumatologia@gmail.com

Vilma S. T. Viana
visatv@gmail.com

Sandra G. Pasoto
sandra.pasoto@hc.fm.usp.br

Elaine P. Leon
e.leon@fm.usp.br

Eloisa Bonfa
eloisa.bonfa@hc.fm.usp.br

1 Division of Rheumatology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

2 Present address: Universidade Federal de Alfenas, Alfenas, Brazil

3 Disciplina de Reumatologia, Universidade de São Paulo, Avenida Dr. Arnaldo 455, sala 3142, Cerqueira César, Sao Paulo, SP 01246-903, Brazil

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by marked skin and internal organ fibrosis and vascular dysfunction. It shows a heterogeneous clinical presentation associated with various immunological abnormalities [1] and ethnical differences [2–5]. Previous publications suggest that African-American SSc patients present earlier age at disease onset and more severe organ involvement, represented mainly by interstitial lung disease (ILD), contributing to a worse survival, when compared to white SSc patients [6]. The reported increased expression of pro-fibrotic factors (TGF-β) and reduced expression of anti-fibrotic factors (caveolin-1, HGF, and PPAR-γ) in blacks compared to whites with SSc may account for this racial disparity [7].

An important characteristic of SSc is the presence of specific antibodies directed against nuclear proteins. Anti-topoisomerase I (anti-Scl70), anti-centromere, and anti-RNA polymerase III, the most important specific SSc autoantibodies, are knowingly related to distinct clinical characteristics [1, 8, 9] and were included in the variables presented in the 2013 classification criteria for SSc [10]. The presence of anti-Scl70 is related to severe ILD [8], being more frequent in African-Americans [6], while anti-centromere generally carries a better prognosis and is most commonly found in Caucasians when compared with African-Americans [2, 11]. Anti-RNA polymerase III is usually associated with the diffuse SSc subset and renal crisis [12, 13]. This antibody specificity was detected less frequently in blacks than in whites [6].

Other antibodies against one or more autoantigens include anti-Ku, fibrillarin, Th/To, and PM-Scl and can be found associated with distinctive clinical correlations [1, 8]. Anti-fibrillarin is more frequent in African-Americans when compared to white SSc patients [2], as well as it is associated with younger age at disease onset and higher frequency of diffuse cutaneous involvement and pulmonary hypertension (PH) [14].

There are very limited reports regarding the influence of race in Latin-American SSc patients with distinctive features in Mexican mestizos [15] and no data for African-Brazilian SSc patients. Taking into consideration that the degree of miscegenation in Brazil is very high, it provides a unique opportunity to improve our understanding on the impact of ethnic factors on Brazilian SSc black patients. We therefore investigated herein if the distinctive clinical and laboratorial features between blacks and whites reported for other SSc populations remains in this context.

Material and methods

Patients Serum samples from 260 consecutive SSc adult patients were selected from 328 patients followed at the Scleroderma Outpatient Clinic of the Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo, Brazil, from 2000 to 2010, to characterize the autoantibody profile. Clinical and demographic features of the patients were assessed on an electronic register database platform. All patients fulfilled 2013 ACR/EULAR classification criteria for SSc [10]. Patients were also classified as *limited SSc* and *diffuse SSc* according to LeRoy et al. criteria [16]. Patients with rheumatoid arthritis (RA), idiopathic inflammatory myositis, systemic lupus erythematosus (SLE), or Sjogren syndrome (SS) in overlap with SSc were excluded. Disease onset was defined according to the age at which the first non-Raynaud's manifestation of SSc occurred. Ethnic groups of SSc patients were defined according the self-reported ethnicity of parents and all four grandparents and they were categorized as whites (only European ancestry) and African-Brazilians (patients with at least one African ancestor) [17]; patients who failed to fit in any of the two established ethnic groups were excluded from the analysis.

Clinical features Clinical organ involvement attributable to SSc was determined according to the following criteria: (1) *Calcinosis*: subcutaneous calcifications of the skin observed either on physical examination or by radiography of the affected area; (2) *Telangiectasias*: visible macular dilated superficial blood vessels, with collapse upon pressure and fill slowly when pressure is released; (3) *Digital ulcers*: ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma; (4) *Joint*: arthritis and/or tendon friction rubs; (5) *Muscle*: proximal muscle weakness and elevated serum creatine kinase concentration or myopathic changes on electromyography or evidence of myositis on muscle biopsy; (6) *Esophagus*: defined as hypomotility or reduced lower esophageal sphincter pressure causing gastroesophageal reflux and dyspepsia assessed by esophagogram, manometry, or endoscopy; (7) *Intestines*: diarrhea due to intestinal bacterial overgrowth, intestinal dysmotility, pseudo-obstruction, or gastrointestinal blood loss resulted from mucosal telangiectasia; (8) *ILD*: defined by any fibrosis or ground glass changes in chest high-resolution computed tomography (HRCT) or forced vital capacity (FVC) < 70%; patients were considered as *severe ILD* when ground-glass > 10% in chest HRCT and/or FVC ≤ 50%; (9) *PH*: defined by mean pulmonary arterial pressure > 25 mmHg by heart catheterization or pulmonary artery systolic pressure > 40 mmHg by echocardiogram; (10) *Heart*: defined as left-sided congestive heart failure (FEVI < 45%) or pericarditis by echocardiogram, arrhythmia, or conduction defect; (11) *Kidney*: "renal crisis," defined as malignant hypertension associated with rapidly progressive renal failure without any other cause; and (12) *Neurologic*: defined as polyneuropathy by electroneuromyography.

The magnitude and severity of skin thickening were evaluated by the modified Rodnan skin score that analyzes 17 anatomical sites, graded from 0 (normal skin) to 3 (intense skin thickening) [18].

Survival All causes and ages of death, as well as the number of patients who lost follow-up, from January 2000 to December 2018, were analyzed. Before death patients were regularly followed in our SSc outpatient clinic. Patient outcome was considered according to their last visit to the Scleroderma Outpatient Clinic.

Autoantibodies All serum samples were analyzed for the presence of anti-nuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cells. Autoantibody profile was determined by using a commercial kit (*Systemic Sclerosis [Nucleoli] Autoantibody Profile Euroline [IgG]*, EUROIMMUN Medizimische Labordiagnostika, AG), following the manufacturer's instructions. This line blot kit includes a set of SSc-related targeted autoantigens fixed in membrane strips: Scl70, CENP-A/CENP-B, RNA polymerases III, Ku, fibrillarin, Th/To, and PM-Scl75/PM-Scl100. Results were interpreted blindly to the clinical status based on the signal intensity of the immunoreactivity to the different antigens fixed on the strips as detected by EUROLineScan software: negative (no signal), borderline (+), and positive (signal varying from + to +++). All serum samples analyzed herein were used after obtaining the informed consent of all patients.

Data analysis Statistical analysis was performed using SPSS version 23. *T* test was applied for continuous variables, chi-square, and Fisher's exact test for comparison of the frequencies. p values ≤ 0.05 were considered statistically significant with confidence interval of 95%. Survival was assessed by Kaplan–Meier analysis and associations with mortality by Cox proportional hazards using age, gender, and SSc disease subset.

Results

Comparison of African-Brazilian and white SSc patients The demographic, clinical, and serological features of 57 African-Brazilians and 203 white SSc patients are illustrated in Table 1. African-Brazilian SSc patients presented shorter disease duration (12.8 ± 6.5 vs. 15.9 ± 8.1 years, $p = 0.009$) as well as a statistical trend to an earlier age of onset (40 ± 12.2 vs. 41.9 ± 14.6 years, $p = 0.056$) when compared to white patients. Both ethnic groups presented a predominance of limited SSc ($p > 0.05$). Raynaud's phenomenon (99% vs. 100%), esophageal involvement (92% vs. 88%), ILD (71% vs. 72%), and digital ulcers (72% vs. 66%) were the clinical manifestation most commonly found in both groups of patients. Severe ILD was significantly more frequent in African-Brazilian patients (58% vs. 43%; $p = 0.044$). A trend to higher frequency of death in African-Brazilians compared to whites was also observed (26% vs. 16%, $p = 0.084$). Further comparison of serological characteristics revealed that frequency of ANA was high and comparable in both groups (88% vs. 88%, $p = 0.994$). The nucleolar ANA pattern was significantly more frequent in African-Brazilians (28% vs. 13%, $p = 0.008$), whereas the centromeric ANA pattern was more frequent in whites (29% vs. 14%, $p = 0.026$). Other patterns such as nuclear homogeneous/nucleolar (16% vs. 21%, $p = 0.410$), nuclear homogeneous (16% vs. 12%, $p = 0.492$), nuclear speckled (11% vs. 10%, $p = 0.968$), and fine dense speckled (2% vs. 1%, $p = 0.526$) had lower and comparable frequencies among groups. Regarding specific SSc antibodies, only CENP-B was less frequent in African-Brazilians (18% vs. 34%, $p = 0.017$) with a similar trend for CENP-A (18% vs. 30%, $p = 0.079$).

Comparison of African-Brazilians and whites according to SSc subsets The comparison of demographic, clinical, and autoantibodies in African-Brazilians and white patients according to the SSc subsets are shown in Table 2.

African-Brazilian patients with diffuse SSc had a higher frequency of PH (24% vs. 6%; $p = 0.017$), heart involvement (24% vs. 7%; $p = 0.037$), and higher mortality (48% vs. 19%; $p = 0.0009$) than whites. The former group had a higher frequency of nucleolar ANA pattern (33% vs. 13%, $p = 0.036$) and anti-fibrillarin antibodies (24% vs. 7%, $p = 0.037$).

African-Brazilian patients with limited SSc had a shorter mean disease duration (12.9 ± 7.0 vs. 16.3 ± 8.4 years, $p = 0.026$), with lower frequency of esophageal involvement (82% vs. 91%; $p = 0.05$) compared to white patients. Anti-centromeric antibodies (22% vs. 40%, $p = 0.049$) were less frequently detected in African-Brazilians with limited subset, with a similar trend of lower frequency for anti-CENP-B (28% vs. 45%, $p = 0.060$).

Survival analysis In the long-term follow-up (2000–2018), 48 patients died (33 whites and 15 African-Brazilians). The causes of death were the following: 18 ILD, 8 infection, 6 PH, 6 heart, and 10 other causes (multiple organ failure, stroke, chronic kidney failure, cancer, sudden death). In 30 patients, death was considered as related to SSc and 34 lost follow-up. Death was more frequent in African-Brazilians (26% vs. 16%; $p = 0.084$), and the lower mean age of death in this group of patients compared to whites did not reach

Table 1 Comparison of demographic, clinical, and serological features of 57 African-Brazilian and 203 white SSc patients

	African-Brazilian ($n = 57$)	White ($n = 203$)	OR (95%CI)	*p*
Demographic				
Mean age at onset (years)	40.0 (± 12.2)	41.9 (± 14.6)	1.51 (0.83–2.76)	*0.056*
Mean disease duration (years)	12.8 (± 6.5)	15.9 (± 8.1)	1.64 (0.85–3.15)	*0.009*
% female	50 (88)	183 (90)	1.02 (0.92–1.14)	0.595
Clinical				
Modified RSS (mean ± SD)	10.4 (± 13.1)	9.6 (± 11.3)	1.17 (0.61–2.26)	0.097
Diffuse subset (%)	21 (37)	68 (34)	0.90 (0.61–1.34)	0.638
Limited subset (%)	36 (63)	135 (67)	1.05 (0.84–1.31)	
Raynaud's phenomenon	57 (100)	200 (99)	0.98 (0.96–1.00)	1.000*
Digital ulcers (%)	41 (72)	134 (66)	0.91 (0.75–1.11)	0.400
Calcinosis (%)	8 (14)	40 (20)	1.40 (0.69–2.82)	0.330
Telangiectasia (%)	30 (53)	130 (64)	1.21 (0.93–1.58)	0.118
Joint (%)	16 (28)	37 (18)	0.64 (0.39–1.07)	0.103
Muscle (%)	5 (9)	16 (8)	0.89 (0.34–2.34)	0.827
Esophagus (%)	50 (88)	186 (92)	1.05 (0.94–1.16)	0.368
Intestines (%)	5 (9)	19 (9)	1.06 (0.41–2.73)	0.892
ILD (%)	41 (72)	144 (71)	0.98 (0.82–1.18)	0.884
Severe ILD	33 (58)	87 (43)	1.83 (1.01–3.23)	*0.044*
PH (%)	8 (14)	26 (13)	0.93 (0.43–1.90)	0.808
Heart (%)	9 (16)	23 (11)	0.71 (0.35–1.46)	0.365
Kidney (%)	2 (3.5)	1 (0.5)	0.14 (0.13–1.52)	0.122*
Neurologic (%)	4 (7)	15 (7)	0.94 (0.30–2.97)	0.924
Death (%)	15 (26)	33 (16)	1.84 (0.91–3.69)	*0.084*
Laboratorial				
ANA	50 (88)	178 (88)	1.00 (0.89–1.11)	0.994
Centromeric (%)	8 (14)	58 (29)	2.00 (1.03–4.01)	*0.026*
Nucleolar (%)	16 (28)	27 (13)	2.50 (1.25–5.15)	*0.008*
Autoantibodies				
Anti-Scl70 (%)	17 (30)	62 (31)	1.02 (0.65–1.61)	0.900
Anti-CENP-B (%)	10 (18)	69 (34)	1.93 (1.06–3.51)	*0.017*
Anti-CENP-A (%)	10 (18)	59 (30)	1.66 (0.91–3.04)	0.079
Anti-RNA pol III (%)	2 (4)	10 (5)	1.40 (0.31–6.22)	0.652
Anti-PM-Scl75 (%)	7 (12)	27 (13)	1.08 (0.50–2.36)	0.830
Anti-PM-Scl100 (%)	4 (7)	11 (5)	0.77 (0.25–2.33)	0.647
Anti-fibrillarin (%)	8 (14)	23 (11)	0.80 (0.38–1.70)	0.578
Anti-Th/To (%)	1 (2)	11 (5)	3.08 (0.40–23.42)	0.244
Anti-Ku (%)	3 (5)	7 (3)	0.65 (0.17–2.45)	0.529

ILD interstitial lung disease, *PH* pulmonary hypertension, *SD* standard deviation, *RSS* Rodnan skin score, *CI* confidence interval

*Fisher exact text

statistical significance (55 ± 11.8 vs. 62.3 ± 16.8, $p = 0.092$). Regarding clinical subset, death was significantly more frequent in African-Brazilians with diffuse SSc (48% vs. 19%; $p = 0.009$) but not with limited SSc (14% vs. 15%; $p = 0.889$).

The cumulative survival rate was 97%, 89%, 82%, and 77% for whites and 89%, 80%, 67%, and 49% for African-Brazilians in 5, 10, 15, and 20 years, respectively (log-rank $p = 0.027$) (Fig. 1). After considering COX in unadjusted model, African-Brazilians had a significantly higher relative risk (RR) of death than whites (RR 1.96, CI 95% 1.06–3.63, $p = 0.031$). When adjusted by age, there was an increase in the risk (RR = 2.19, CI 95% 1.17–4.10, $p = 0.013$). After adjusted by age, gender, and SSc disease subset, African-Brazilians maintained a higher mortality rate compared to whites (RR 2.06, CI 95% 1.10–3.83, $p = 0.023$).

Table 2 Comparison of the clinical and demographic characteristics of white and African-Brazilian SSc patients according to clinical subset

	Diffuse SSc (*n* = 89)			Limited SSc (*n* = 171)		
	African-Brazilian (*n* = 21)	White (*n* = 68)	*p*	African-Brazilian (*n* = 36)	White (*n* = 135)	*p*
Demographic						
Mean age at onset (years)	37.4 (± 13.3)	35.1 (± 14.2)	0.611	41.6 (± 11.5)	45.4 (± 13.6)	0.249
Mean disease duration (years)	12.7 (± 5.7)	15.0 (± 7.6)	0.197	12.9 (± 7.0)	16.3 (± 8.4)	*0.026*
% Female	16 (76)	56 (82)	0.530	34 (94)	127 (94)	0.933
Clinical						
Modified RSS (mean ± SD)	21.5 (± 12.7)	19.8 (± 11.3)	0.351	3.5 (± 3.5)	4.1 (± 6.6)	0.758
Raynaud's phenomenon	21 (100)	68 (100)	–	36 (100)	132 (98)	1.000*
Digital ulcers (%)	16 (76)	52 (77)	0.979	25 (69)	82 (61)	0.338
Calcinosis (%)	3 (14)	12 (18)	0.719	5 (14)	28 (21)	0.355
Telangiectasia (%)	9 (43)	40 (59)	0.199	21 (58)	90 (67)	0.352
Joint (%)	6 (29)	9 (13)	0.101	10 (28)	28 (21)	0.367
Muscle (%)	1 (5)	8 (12)	0.352	4 (11)	8 (6)	0.279
Esophagus (%)	21 (100)	62 (91)	0.329*	29 (81)	124 (92)	*0.050*
Intestines (%)	4 (19)	8 (12)	0.393	1 (3)	11 (8)	0.262
ILD (%)	18 (86)	55 (81)	0.614	23 (64)	89 (66)	0.819
Severe ILD	17 (81)	44 (65)	0.161	16 (44)	43 (32)	0.158
PH (%)	5 (24)	4 (6)	*0.017*	3 (8)	22 (16)	0.230
Heart (%)	5 (24)	5 (7)	*0.037*	4 (11)	18 (13)	0.723
Kidney (%)	2 (10)	1 (2)	0.137*	0 (0)	0 (0)	–
Neurologic (%)	3 (14)	6 (9)	0.468	1 (3)	9 (7)	0.377
Death (%)	10 (48)	13 (19)	*0.009*	5 (14)	20 (15)	0.889
Laboratorial						
ANA	17 (81)	57 (84)	0.759	33 (92)	121 (90)	0.717
Centromeric (%)	0 (0)	4 (6)	0.569	8 (22)	54 (40)	*0.049*
Nucleolar (%)	7 (33)	9 (13)	*0.036*	9 (25)	18 (13)	0.088
Autoantibodies						
Anti-Scl70 (%)	8 (38)	35 (52)	0.284	9 (25)	27 (20)	0.527
Anti-CENP-B (%)	0 (0)	8 (12)	0.099	10 (28)	61 (45)	*0.060*
Anti-CENP-A (%)	0 (0)	5 (7)	0.334	10 (28)	54 (40)	0.169
Anti-RNA pol III (%)	2 (10)	6 (9)	0.922	0 (0)	4 (3)	0.580
Anti-PM-Scl75 (%)	1 (5)	9 (13)	0.282	6 (17)	18 (13)	0.621
Anti-PM-Scl100 (%)	1 (5)	3 (4)	1.000	3 (8)	8 (6)	0.601
Anti-fibrillarin (%)	5 (24)	5 (7)	*0.037*	3 (8)	18 (13)	0.417
Anti-Th/To (%)	0 (0)	2 (3)	1.000	1 (3)	9 (7)	0.377
Anti-Ku (%)	1 (5)	2 (3)	0.559	2 (6)	5 (4)	0.618

ILD interstitial lung disease, *PH* pulmonary hypertension, *RSS* Rodnan skin score, *SD* standard deviation

*Fischer's exact text

Discussion

The present study, focusing on highly miscegenated African-Brazilian SSc patients, showed that there are major differences in the clinical and serologic presentations between this group and whites and suggests that these distinct clinical profiles can vary according to the SSc subsets and the different SSc specific autoantibodies.

The 2010 national census showed that the Brazilian population is composed by 50.6% of African-Brazilians (43.6% "pardos" and 7.0% non-miscegenated blacks), 48.7% of whites, and 0.7% of Asian ancestry and Indians [19]; these

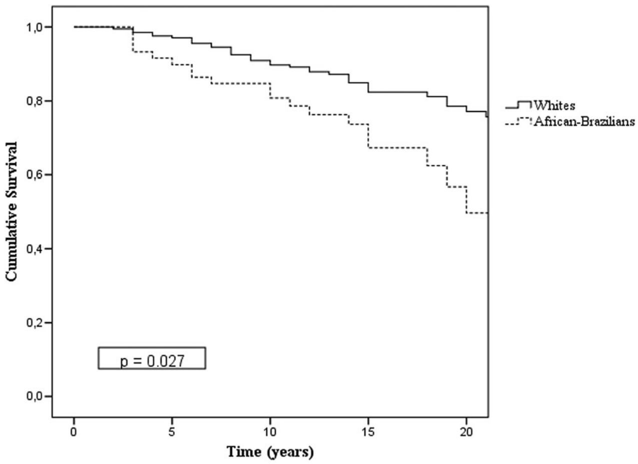

Fig. 1 Kaplan–Meier cumulative survival by ethnic groups

pardos are originated from the miscegenation between whites and blacks. This large population with black ancestry was originated from the significant miscegenation of African slaves brought to Brazil from the 16th to the 19th centuries with the white population of predominantly European ancestry. This large "migration" of diverse African populations, predominantly from West Africa, to Europe and Americas (especially Brazil and USA), contributed to the significantly heterogeneous genetic pool of these black populations [20]. This manifest itself by the predominant European genomic ancestry (> 70%) in Brazilian whites irrespective of geographical region and the average almost 40% European genomic ancestry in African-Brazilians with a range of 68.6 to 42.2% [21].

Despite the similar percentage of whites and African-Brazilians in the Brazilian population, we found a significant predominance of white patients in our cohort, from the southwestern Brazilian region. The only study analyzing incidence (11.9 per million) and prevalence (105.6 per million) of SSc in Brazil included 89 patients in the State of Mato Grosso (Midwest region); according to ethnicity, there were 65.2% whites and 31.4% black/ brown patients [22]. This predominance of white patients was also observed in another Brazilian cohort, from the south region [23]. A national study focusing on the comparison of SSc cohorts in distinct Brazilian regions is necessary to better understand how the heterogeneity of the Brazilian population can affect SSc clinical and laboratory presentation.

It is known that ethnic differences can influence disease presentation among distinct populations [2, 3, 5, 24, 25]. Although most studies focused in a predominant Caucasian SSc population [26, 27], reports focusing black populations showed a more severe disease in African-Americans [4, 6, 28]. Small studies in sub-Saharan African populations are rare, analyzing black patients from South Africa 29] and Nigeria [30].

The analysis of the demographic data showed similarities and differences among African-Brazilians and African-Americans. The percentage of the former group in this cohort was 22% (260 patients), while the percentage of African-Americans varied in different studies, from 6.4% in the Pittsburgh cohort (3148 patients) [6], 9.4% in the Johns Hopkins cohort (2217 patients) [4], 17% in Texas (168 patients) [2], and 22.8% in Florida (105 patients) [31]. For both ethnic groups, female gender was overrepresented in comparison to male. In contrast to African-Americans in whom diffuse SSc is the dominant subtype [2, 4, 6, 28], in the African-Brazilian cohort, the limited SSc subset was more frequent in both ethnic groups. But in line with the former group, African-Brazilians also had worse prognosis and a trend to early age at onset [4, 6].

African-American ethnicity is recognized one of the main significant factors associated with ILD in SSc patients [32]. This higher prevalence of lung involvement in black SSc patients seems to be directly linked to the expression of autoantibodies. The Pittsburg cohort compared 203 African-Americans with 2945 Caucasians and showed that anti-Scl70 positive African-Americans presented a higher frequency of ILD than Caucasians [6], which was corroborated by latter studies in African-Americans [28] and South-Africans [33]. Although ILD was quite frequent (> 70%) when considering any ground glass in both SSc subsets in this study, it is important to point out that a significant association with African-Brazilian ethnicity was observed when the subgroup of severe ILD was analyzed separately.

Interestingly, with this study design, we found that PH and heart involvement were more frequent in the diffuse SSc subset in African-Brazilians, a previously known association observed in some African-American cohorts [28, 34]. The severity of PAH in different ethnicities was analyzed in a study of 160 consecutive SSc patients (131 whites and 29 African-Americans) from the Johns Hopkins cohort; African-American patients presented worse functional class associated to worse survival compared to white patients (62% vs. 73% at 2 years and 26% vs. 44% at 5 years) [35]. Our group has also shown that race may impact 6-min walking distance (6MWD) in SSc patients, with African-Brazilian patients walking shorter distances than whites [36].

The single-center setting of this study allowed a more uniform definition of the clinical parameters and the use of the same laboratory methodology for autoantibody analysis. We used line immunoassay (LIA), and this method was described to be more practical and efficient than traditional immunoprecipitation to detect anti-nuclear antibodies in routine practice, greatly improving sensitivity in SSc diagnosis [37].

An important serologic difference between black and white SSc patients, also observed in the present study, is the finding of nucleolar ANA pattern association with black population and the centromeric ANA pattern with white SSc patients [26, 28, 38]. Taking into consideration that clinical features and ethnicity are strongly associated with autoantibodies in SSc, we hypothesized that distinct ANA patterns would occur in our miscegenated population. Reinforcing this possibility, a recent publication from the International Consensus on ANA Patterns (ICAP) has proposed 29 distinct ANA patterns; among them, three nucleolar patterns (homogeneous, clumpy, and punctate) were described and, more importantly, have characterized that SSc autoantibodies, such as anti-fibrillarin, anti-Th/To, anti-PM/Scl, and anti-RNA polymerase III, are associated with the nucleolar ANA pattern [39]. Although this study did not analyze the distinct nucleolar patterns, we found that all patients with positive anti-fibrillarin or anti-Th/To or anti-PM/Scl presented nucleolar ANA pattern, with anti-RNA polymerase III displaying nucleolar or large speckled ANA patterns, similar to the ICAP findings.

Among the other SSc autoantibodies, only anti-fibrillarin showed significant results, as it was associated with diffuse SSc African-Brazilian patients with nucleolar ANA pattern, PH, and heart involvement. This higher prevalence in African-American SSc patients was already described [6, 14], and a specific multicenter study in USA with 278 African-American patients showed an association between anti-fibrillarin and younger age of disease onset, digital ulcers, diarrhea, and pericarditis, as well as HLA-DRB1*0804 [14]. The other specific SSc autoantibodies, including anti-RNA polymerase III, were present in less than 5% of the studied patients, not allowing any statistical analysis. A recent study analyzing a large multicenter cohort of 1000 SSc patients in USA found that anti-RNA polymerase III, anti-Th/To, and anti-PM/Scl did not differ significantly among the ethnic groups [38].

We have found that the cumulative survival rate in the African-Brazilians (from 89% at 5 years to 49% at 20 years) was significantly worse than that observed in the white patients (from 97% at 5 years to 77% at 20 years), especially in patients with diffuse SSc. The African-Brazilians also have a trend to younger age at onset and at death compared to the whites. Of note, the diverse ethnic background with a high proportion of European ancestry did not reverse the worse prognosis observed for African-Brazilians which is in agreement with findings in distinct African-American cohorts [4, 6, 28]. In the Pittsburgh cohort (3148 patients), survival curves were significantly worse in African-Americans (66% at 5 years and 51% at 10 years) when compared to white (75% at 5 years and 60% at 10 years) SSc patients [6]. The 10-year mortality rate in the Johns Hopkins cohort (2217 patients) was 43% among African-Americans and 35% among whites [4]. Another Brazilian study, analyzing 96 SSc patients, did not analyze the influence of ethnicity in SSc, due to the low number of African-Brazilian patients (20 patients—22%) [23].

This study has a few limitations including the small number of African-Brazilians (57 patients) and the definition of African-Brazilian according solely to at least one African ancestor among parents and grandparents [17]. Although the worse survival rate observed in the African-Brazilians can be associated to the higher frequency of ILD, PH, and heart involvement observed in these patients, the impact of the socio-economic status, not evaluated in this study, is a relevant confounding variable in understanding health disparities in our country.

In conclusion, African-Brazilian SSc patients, despite their high frequency of European ancestry, have distinct features compared to whites. African-Brazilians with diffuse subtype have a more severe presentation characterized by a higher frequency of death, PH, heart involvement, and nucleolar antibodies, as well as an association with severe ILD. Conversely, a lower frequency of anti-centromeric antibodies was observed for African-Brazilians with limited subtype. This pattern is similar to the reported for less miscegenated black population, suggesting that other factors may play a more relevant role in SSc health disparities.

Authors' contribution CM collected the data, performed the statistical analysis, analyzed the results, and wrote the manuscript; VST and EPL supervised the laboratory data and analysis; SGP contributed to the writing and critically reviewed the manuscript; EB and PDSB designed, analyzed the results, critically reviewed the manuscript, and wrote the final version. All authors read and approved the final manuscript.

Funding This work was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP #2015/03756-4 to E.B.), Conselho Nacional de Desenvolvimento Científico e Tecnológico (#3053068/2014 to E.B.), and Federico Foundation (to P.D.S.B. and E.B.).

Compliance with ethical standards

This study was approved by the local research ethics committee (no. 1.627.446).

Disclosures None.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Nihtyanova SI, Denton CP (2010) Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol 6:112–116
2. Reveille JD, Fischbach M, McNearney T, Friedman AW, Aguilar MB, Lisse J, Fritzler MJ, Ahn C, Arnett FC (2001) Systemic sclerosis in 3 US ethnic groups: a comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. Semin Arthritis Rheum 30:332–346

3. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O et al (2007) Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 66:754–763
4. Gelber AC, Manno RL, Shah AA, Woods A, Le EN, Boin F et al (2013) Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins scleroderma center and review of the literature. Medicine (Baltimore) 92:191–205
5. Proudman SM, Huq M, Stevens W, Wilson ME, Sahhar J, Baron M, Hudson M, Pope J, Allanore Y, Distler O, Kowal-Bielecka O, Matucci-Cerinic M, Low AHL, Teng GG, Law WG, Santosa A, Nikpour M, Australian Scleroderma Interest Group (ASIG), Canadian Scleroderma Research Group (CSRG), EULAR Scleroderma Trials and Research group (EUSTAR), Singapore Scleroderma Workgroup (SCORE) (2017) What have multicentre registries across the world taught us about the disease features of systemic sclerosis? J Scleroderma Relat Disord 2:169–182
6. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA Jr (2012) A clinical and serologic comparison of African-American and Caucasian patients with systemic sclerosis. Arthritis Rheum 64: 2986–2994
7. Silver R, Bogatkevich G, Tourkina E, Nietert P, Hoffman S (2013) Racial differences between blacks and whites with systemic sclerosis. Curr Opin Rheumatol 24:642–648
8. Ho KT, Reveille JD (2003) The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther 5:80–93
9. Steen VD (2005) Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 35:35–42
10. Van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al (2013) 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 65: 2737–2747
11. McNeilage LJ, Youngchaiyud U, Whittingham S (1989) Racial differences in antinuclear antibody patterns and clinical manifestations of scleroderma. Arthritis Rheum 32:54–60
12. Bunn CC, Denton CP, Shi-Wen X, Knight C, Black CM (1998) Anti-RNA polymerases and other autoantibody specificities in systemic sclerosis. Br J Rheumatol 37:15–20
13. Kuwana M, Okano Y, Pandey JP, Silver RM, Fertig N, Medsger TA (2005) Enzyme-linked immunosorbent assay for detection of anti-RNA polymerase III antibody: analytical accuracy and clinical associations in systemic sclerosis. Arthritis Rheum 52:2425–2432
14. Sharif R, Fritzler MJ, Mayes MD, Emilio B, McNearney TA, Draeger H et al (2012) Anti-fibrillarin antibody in African American patients with systemic sclerosis: Immunogenetics, clinical features, and survival analysis. J Rheumatol 38:1622–1630
15. Rodriguez-Reyna TS, Hinojosa-Azaola A, Martinez-Reyes C, Nuez-Alvarez CA, Torrico-Lavayen R, Garca-Hernndez JL, Cabiedes-Contreras J (2011) Distinctive autoantibody profile in Mexican Mestizo systemic sclerosis patients. Autoimmunity 44: 576–584
16. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell NWF (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15: 202–205
17. Gomes RC, Silva MF, Kozu K, Bonfá E, Pereira E, Terreri MT et al (2016) Features of 847 childhood-onset systemic lupus erythematosus patients in three age groups at diagnosis: a Brazilian multicenter study. Arthritis Care Res 68:1736–1741
18. Furst DE, Clements PJ, Steen VD, Medsger TA Jr, Masi AT, D'Angelo WA et al (1998) The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. J Rheumatol 25:84–88
19. IBGE (2010) Censo Demográfico 2010. Características da População e dos Domicílios. Inst Bras Geografia Estatística 48
20. Tishkoff SA, Williams SM (2002) Genetic analysis of African populations: human evolution and complex disease. Nat Rev Genet 3: 611–621
21. Pena SDJ, Di Pietro G, Fuchshuber-Moraes M, Genro JP, Hutz MH, Kehdy FS et al (2011) The genomic ancestry of individuals from different geographical regions of Brazil is more uniform than expected. PLoS One 6:e17063
22. Horimoto AMC, Matos EN, Costa MR, Takahashi F, Rezende MC, Kanomata LB et al (2017) Incidence and prevalence of systemic sclerosis in Campo Grande, State of Mato Grosso do Sul, Brazil. Rev Bras Reumatol 57:107–114
23. Müller CDS, Paiva S, Azevedo VF (2011) Autoantibody profile and clinical correlation in a group of patients with systemic sclerosis in southern. Brazil. 51(4):314–324
24. Kuwana M, Okano Y, Kaburaki J, Tojo T, Medsger TA (1994) Racial differences in the distribution of systemic sclerosis-related serum antinuclear antibodies. Arthritis Rheum 37:902–906
25. Meyer OC, Fertig N, Lucas M, Somogyi N, Medsger TA (2007) Disease subsets, antinuclear antibody profile, and clinical features in 127 French and 247 US adult patients with systemic sclerosis. J Rheumatol 34:104–109
26. Meier FMP, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, Allanore Y, Distler O, Riemekasten G, Valentini G, Müller-Ladner U, EUSTAR Co-authors (2012) Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 71:1355–1360
27. Patterson KA, Roberts-Thomson PJ, Lester S, Tan JA, Hakendorf P, Rischmueller M, Zochling J, Sahhar J, Nash P, Roddy J, Hill C, Nikpour M, Stevens W, Proudman SM, Walker JG (2015) Interpretation of an extended autoantibody profile in a well-characterized Australian systemic sclerosis (scleroderma) cohort using principal components analysis. Arthritis Rheumatol 67: 3234–3244
28. Morgan ND, Shah AA, Mayes MD, Domsic RT, Medsger TA Jr, Steen VD et al (2017) Clinical and serological features of systemic sclerosis in a multicenter African American cohort analysis of the genome research in African American scleroderma patients clinical database. Medicine (Baltimore) 51:e8980
29. Tager RE, Tikly M (1999) Clinical and laboratory manifestations of systemic sclerosis (scleroderma) in Black South Africans. Rheumatology 38:397–400
30. Adelowo OO, Oguntona S (2009) Scleroderma (systemic sclerosis) among Nigerians. Clin Rheumatol 28:1121–1125
31. Krzyscczak M, Li Y, Ross SJ, Ceribelli A, Chan EKL, Bubb MR et al (2011) Gender and ethnicity differences in the prevalence of scleroderma-related antibodies. Clin Rheumatol 30:1333–1339
32. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N et al (2007) Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Care Res 57:318–326
33. Ashmore P, Tikly M, Wong M, Ickinger C (2018) Interstitial lung disease in South Africans with systemic sclerosis. Rheumatol Int 38:657–662
34. Laing TJ, Gillespie BW, Toth MB, Mayes MD, Gallavan RH Jr, Burns CJ et al (1997) Racial differences in scleroderma among women in Michigan. Arthritis Rheum 40:734–742
35. Blanco I, Mathai S, Shafiq M, Boyce D, Kolb TM, Chami H et al (2014) Severity of systemic sclerosis-associated pulmonary arterial hypertension in African Americans. Medicine (Baltimore) 93:177–185
36. Villalba WO, Sampaio-Barros PD, Pereira MC, Cerqueira EMFP, Leme CA, Marques-Neto JF, Paschoal IA (2007) Six-minute walk

test for the evaluation of pulmonary disease severity in scleroderma patients. Chest 131:217–222

37. Villalta D, Imbastaro T, Di Giovanni S, Lauriti C, Gabini M, Turi MC, Bizzaro N (2012) Diagnostic accuracy and predictive value of extended autoantibody profile in systemic sclerosis. Autoimmun Rev 12:114–120

38. Nandiwada SL, Peterson LK, Mayes MD, Jaskowski TD, Malmberg E, Assassi S, Satoh M, Tebo AE (2016) Ethnic differences in autoantibody diversity and hierarchy: more clues from a US cohort of patients with systemic sclerosis. J Rheumatol 43: 1816–1824

39. Damoiseaux J, Andrade LEC, Carballo OG, Konrad K, Francescantonio PLC, Fritzler MJ et al (2019) Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. https://doi.org/10.1136/annrheumdis-2018-214436