Clinical and serological features of systemic sclerosis patients, according to different geographic areas: insights from an observational, cross-sectional study of two independent cohorts

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Abstract

Objective

To evaluate the clinical, and serological features and treatments in two independent cohorts of Italian and Egyptian systemic sclerosis (SSc) patients, according to geographic areas.

Methods

3 Italian and 5 Egyptian centres participated in patient recruitment in 2017. The demographic, clinical, and serological data were collected and defined according to the previously developed severity score and activity index. The database included 261 consecutive Italian patients (242 women/19 men) and 197 Egyptian patients (177 women/20 men), all of whom fulfilled the classification criteria of ACR/EULAR 2013 and criteria proposed by LeRoy and Medsger.

Results

Egyptians were younger, had an earlier onset of both the first non-Raynaud's and Raynaud's phenomenon and a more severe modified skin score. A greater percentage of Egyptians had the active form of the disease, a pulmonary arterial pressure estimated by echocardiography>35mmHg than Italians and interstitial lung disease. The severity score was higher in Egyptians, the frequency of anti-topoisomerase I (ATA) was higher in Italians, and Egyptians were more likely to be negative for both anticentromere and ATA antibodies than Italians. Egyptians had higher rates of synthetic disease-modifying antirheumatic drugs use than Italians; Italians but not Egyptians were under treatment with vasoactive therapy. Notably, Egyptians affected by the limited form of the disease exhibited a more severe clinical course when matched with their Italian counterparts, characterised by higher modified Rodnan skin score (mRSS), more frequent pulmonary involvement, increased frequency of ischaemic digital ulcers, earlier onset of symptoms, and higher severity scores.

Conclusion

Clinical differences may be shown between Italian and Egyptian SSc patients.

Key words

systemic sclerosis, limited cutaneous sclerosis, diffuse cutaneous sclerosis, racial differences

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Received on February 15, 2025; accepted in revised form on April 7, 2025.

Competing interests: none declared.

Introduction

Systemic sclerosis (SSc) is a rare highly heterogeneous autoimmune disorder characterised by microangiopathy, autoimmunity, and abnormal fibrosis, affecting both the skin and internal organs. (1, 2). Clinically, SSc can generally be classified into two forms based on the extent of skin involvement: diffuse cutaneous sclerosis (dcSSc) and limited cutaneous sclerosis (lcSSc) (1, 2). Patients with internal organ involvement and specific SSc autoantibody, but without skin fibrosis are classified as *sine scleroderma* patients (3).

Previous studies suggest that clinical and serological variations exist regarding the severity of SSc patients, according to different geographic areas (4-9). It has been reported that non-European patients, mostly African-American have a more severe disease and increased mortality compared to European patients. Indeed, African-American patients have a higher incidence of the disease, an earlier age of onset, and a higher frequency of cardio-pulmonary complications such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) which are the main causes of morbidity and mortality in SSc (2, 10-12). Differences in the autoantibody profile have also been reported in SSc patients of different geographic areas. In this context, a higher prevalence of the ATA antibody was found in African-American patients while a higher prevalence of the anticentromere (ACA) antibody was found in European patients (13). It is well known that the presence of ATA is correlated with a higher frequency of ILD in patients with dcSSc while the ACA is mostly correlated with PAH in patients with lcSSc. RNA polymerase III antibody (anti-Pol III) is often mutually exclusive of ATA and ACA, thus the most frequent antinuclear antibody (ANA) in SSc after ACA and ATA is strongly associated with the dcSSc form of the disease and scleroderma renal crisis (14). Regarding anti-Pol III antibody, there is a high variability in prevalence by ethnicity (15) and the frequency of anti-Pol III antibody was found to be lower in African-American patients than in Caucasians (9, 16) with important variations between different countries in Europe (17). However, a study showed that African-American participants of Scleroderma Lung Studies I and II exhibited comparable morbidity and mortality outcomes compared to non-African-American patients, in both short- and long-term assessments. This finding is in contrast with previous observational studies highlighting racial differences, suggesting that the early and aggressive immunosuppressive therapy and follow-up provided at academic centres of excellence for SSc management may play a crucial role (6).

As far as SSc Egyptians are concerned, the results of a cross-sectional study included a small number of SSc patients showing a more severe disease in these patients (18). However, detailed cohort studies on SSc disease presentations in Egyptians compared with other groups are scarce and with a small sample size. To address this gap, our cross-sectional study explores the prevalence of clinical and serologic features and treatment approaches in a sizable cohort of both Italian and Egyptian SSc patients, shedding light on racial differences in the disease according to different geographic areas.

Patients and methods

Study population

The study population included 261 Italian and 197 Egyptian SSc patients from 3 Italian and 5 Egyptian tertiary Rheumatologic Units with high experience in the management of the disease. All patients fulfilled the American College of Rheumatology/European League Against Rheumatism 2013 classification criteria (19) and criteria proposed by LeRoy and Medsger (20) were consecutively enrolled from January 1, 2017, to December 31, 2017. The cross-sectional demographic, clinical, serological data, and treatments were collected and defined according to the previously developed severity score (21) and activity index (22). This study was approved by the ethical committee of Azienda Sanitaria Locale 1 Avezzano-Sulmona-L'Aquila, L'Aquila, Italy (no. 0151147/20) according to the Good Clinical Practice guidelines and the Declaration of Helsinki.

All patients gave their written consent after clearly explaining the study objectives and procedures.

Organ involvement

- Cutaneous subsets

Two groups of SSc patients were established according to LeRoy's 1988 criteria (19), dcSSc and lcSSc. Patients with overlap syndromes were excluded from the study.

- Clinical features

Disease duration was defined as the occurrence of the first non-Raynaud's (non-RP) symptom and the date of visit to each centre. The presence of past/current history of digital ulcers was recorded. According to the modified Rodnan skin score (mRSS), skin thickness was evaluated in 17 body areas (23). SSc-ILD was defined when other possible causes of lung fibrosis were excluded, and bilateral fibrosis confirmed by high resolution computed tomography of the chest (HRCT) and/or restrictive pulmonary abnormalities on pulmonary function tests (PFTs) (TLC<80%) were found. Patients with estimated systolic pulmonary arterial pressure (sPAP)>35mmHg are at higher risk of presenting pulmonary hypertension (PH) with the majority of SSc studies investigating PAH screening used sPAP as a suitable parameter for this goal (24-26). The European Scleroderma Study Group (EScSG) whole series activity index defined the active disease (22). Disease severity was assessed by the core set of variables proposed by Medsger *et al*. (21). The current therapy was also recorded.

- Serological features

ANA were iden- tified by indirect immunofluorescence assay at the local centre's laboratory. ACA and ATA antibodies were also determined.

Statistical analysis

Data were collected and analysed using the statistical package SPSS version 20 SPSS (Inc., Chicago, IL, USA). The description of qualitative variables was by frequencies. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) or median and range interquartile, as appropriate. Categorical variables were expressed as absolute numbers and percentages. Comparisons of continuous variables between the two cohorts, and between the lcSSc and dcSSc forms of the disease, were made by means of utilising the Mann-Whitney U-test. Statistical evaluation was performed using contingency table tests (χ^2-test or Fisher's exact test) to identify significant differences or associations of categorical variables among the two cohorts. *p*-values <0.05 were considered statistically significant.

Table I. Comparison of demographic and disease-specific features between Egyptian and Italian patients.

Feature, n (%)	EGYPTIAN (n=197)	ITALIAN (n=261)	*p*-value
Study population characteristics			
Female	177 (89.8)	241 (92.7)	0.293
Mean age ±SD at disease onset from RP, years	41.18 ± 12.55	58.10 ± 12.17	**<0.0001**
Disease characteristics			
Mean disease duration ± SD from RP onset, years	8.13 ± 6.05	15.6 ± 11.8	**<0.0001**
Mean disease duration ± SD from non-RP onset, years	7.17 ± 6.02	11.89 ± 8.95	**<0.0001**
LcSSc	120 (60.9)	200 (78.4)	**<0.0001**
DcSSc	77 (39.1)	55 (21.6)	**<0.0001**
Autoantibodies			
ANA positive	93% ± 1.6	91.3 ± 0.9	**>0.05**
ACA positive	68 (36.2)	98 (48.5)	**<0.012**
ATA positive	59 (31.4)	99 (49)	**<0.0001**
ACA/ATA negative	61 (32.6)	45 (18.5)	**<0.001**
Organ system Involvement			
mRSS≥14	152 (79.2)	20 (8.4)	**<0.0001**
sPAP>35 mmHg (echocardiogram)	92 (46.7)	35 (13.7)	**<0.0001**
ILD	115 (64.6)	128 (49.6)	**<0.002**
Ulcers (past/current)	186 (94.4)	143 (55.9)	**<0.0001**
EScSG (active disease)	105 (53.3)	27 (11.5)	**<0.0001**

lcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibody; SCL70: anti-topoisomerase I antibody; NON ACA/ATA: anticentromere and anti-topoisomerase I antibodies negative; mRSS: modified Rodnan skin score; sPAP; systolic pulmonary artery pressure estimated by echocardiogram; ILD: interstitial lung disease; EScSG; European Scleroderma Study Group; GI: gastrointestinal.

Results

Study population characteristics

The Italian and Egyptian cohort study population comprised 261 and 197 consecutive SSc patients, respectively. The demographic and disease features are shown in Table I. There was a female preponderance in both cohorts: 241 women (92.7%)/20 men (7.3%) in the Italian cohort, and 177 women (89.8%)/20 men (10.2%) in the Egyptian cohort. The mean age at disease onset was 58.10±12.17 *vs*. 41.18±12.55 years, for the Italian and the Egyptian cohort, respectively.

Disease characteristics

LcSSc was the most frequent subset in both cohorts: 78.4% *vs*. 21.6% in the Italian cohort and 60.9% *vs*. 39.1%; $p<0.001$ for the Egyptians, respectively. Concerning autoantibody status, both ACA and ATA were found higher in Italians than Egyptians (ACA: 48.5% *vs*. 36.2%; $p<0.012$; ATA: 49% *vs*. 31.4%; $p<0.0001$, respectively). Notably, Egyptians were more likely to be negative for both ACA and ATA antibodies than Italians (32.6% *vs*. 18.5%; $p<0.001$). Most patients from both cohorts were ANA positive (93%±1.6 *vs*. 91.3±0.9), respectively for Italians and Egyptians; $p>0.05$).

Egyptians had an earlier onset of RP than Italians (8.13±6.05 *vs*. 15.6±11.8 years; $p<0.0001$) and an earlier appearance of the first non-RP symptom (7.17±6.02 *vs*. 11.9±8.95 years; $p<0.0001$). Past/current history of digital ulcers was more frequent in Egyptians than in Italians (94.4% *vs*. 55.9%; $p<0.0001$). Skin involvement measured by mRSS (mRSS>14) was more frequent in Egyptians than in Italians (79.2% *vs*. 8.4%; $p<0.0001$).

PAPs>35mmHg estimated by echocardiography, a value considered poten-

Table II. Comparison of demographic and disease-specific features of the LcSSc and DcSSc form in Egyptian and Italian patients.

	All LcSSc			All DcSSc		
Feature, n (%)	Egyptian	Italian	*p*-value	Egyptian	Italian	*p*-value
Gender (M)	14 (11.7)	14 (7.1)	0.165	6 (7.8)	4 (7.3)	0.911
Mean age ±SD (yrs)	40.84 ± 13.11	58.34 ± 12.05	**<0.0001**	41.71 ± 11.69	56.34 ± 11.96	**<0.0001**
Disease duration from RP±SD (yrs)	7.67 ± 5.21	16.67 ± 12.18	**<0.0001**	8.84 ± 7.14	13.44 ± 10.12	**<0.003**
Disease duration from non-RP±SD (yrs)	7.03 ± 5.18	11.99 ± 9.23	**<0.0001**	7.38 ± 7.10	11.52 ± 8.011	**<0.003**
ACA positive	65 (54.6)	92 (59)	0.470	3 (4.3)	6 (13.6)	0.075
ATA positive	10 (8.4)	62 (39.7)	**<0.0001**	49 (71)	35 (79.5)	0.311
ACA/ATA negative	44 (37.3)	32 (17.1)	**<0.0001**	17 (24.6)	12 (22.6)	0.797
mRSS>14	80 (67.8)	5 (2.7)	**<0.0001**	72 (97.3)	15 (28.8)	**<0.0001**
EScSG (active)	50 (41.7)	10 (5.7)	**<0.0001**	55 (71.4)	17 (34)	**<0.0001**
ILD	61 (57)	83 (43.5)	**<0.025**	54 (76.1)	43 (78.2)	0.779
PAPs>35mmHg	40 (34.5)	20 (10.5)	**<0.0001**	32 (42.1)	5 (10)	**<0.0001**
Past/current history of ulcers	110 (91.7)	75 (43.6)	**<0.0001**	76 (98.7)	32 (76.2)	**<0.0001**

lcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibody; SCL70: anti-topoisomerase I antibody; NON ACA/ATA: anticentromere and anti-topoisomerase I antibodies negative; mRSS: modified Rodnan skin score; sPAP; systolic pulmonary artery pressure estimated by echocardiogram; ILD: interstitial lung disease; EScSG; European Scleroderma Study Group; GI tract: gastrointestinal tract.

tially associated with PAH, was found more frequently in Egyptians than in Italians (46.7% *vs*. 13.7%; *p*<0.0001). ILD, defined as bilateral fibrosis confirmed by HRCT and/or restrictive pulmonary abnormalities on PFTs, was more frequent in Egyptians than in Italians (64.6% *vs*. 49.6%; *p*<0.002). The EScSG activity index (active disease>3) was found more frequently in Egyptians than in Italians (53.3% *vs*. 11.5%; *p*<0.0001) (Table I).

The severity score was higher in Egyptians than in the Italians, and when patients were categorised according Medsger severity scale (0: normal; 1: mild; 2: moderate; 3: severe; 4: end-stage), there were significant differences between the same category of the two cohorts (data not shown).

Regarding the immunosuppressive regimens, most Egyptians were treated with sDMARDs than Italians (94.4% *vs*. 38.2%; *p*<0.0001). Specifically, methotrexate was widely used in Egyptians than in Italians (53.3% *vs*. 6.4%; *p*<0.0001), followed by hydroxychloroquine (11.2% *vs*. 6.8%; *p*<0.0001), azathioprine (16.2% *vs*. 6.4%; *p*<0.001, and cyclophosphamide (9.6% *vs*. 1.2%; *p*<0.0001). The use of mycophenolate mofetil (MMF) was similar in both cohorts (18.9% *vs*. 13.7%; *p*=0.145). Italians, on the other hand, exhibited higher rates of glucocorticoid low-moderate usage (46.6% *vs*. 32.9%; *p*<0.004). No data were available for the treatment with bDMARDs in Egyptians while only a few Italians (1.2%) were treated with bDMARDS (*p*<0.122).

Regarding vasoactive therapy, both Italians and Egyptians were under treatment with calcium channel blockers (79.5% *vs*. 88.3%; *p*<0.013). Treatment with phosphodiesterase 5 inhibitor was more frequent in Egyptians than in Italians (11.7% *vs*. 1.2%; *p*<0.0001). Notably, no Egyptians were assuming anti-endothelin receptor antagonists, while 11% of Italians were receiving this family of drugs, namely bosentan. Furthermore, 35% of Italians were under treatment with prostacyclin analogs, while no Egyptians were under this kind of treatment (*p*<0.0001). No differences were found for the usage of Angiotensin-Converting Enzyme inhibitors between the two cohorts (30.5% for the Egyptians *vs*. 38.2% for the Italians; *p*<0.09).

Characteristics of the lcSSc and dcSSc form in Egyptian and Italian patients

The demographic and disease-specific features of the lcSSc in Egyptians were compared with those in Italians (Table II). Egyptians with lcSSc were significantly younger (40.84±13.11 *vs*. 58.34±12.05; *p*<0.0001), had a shorter disease duration (7.03±5.18 *vs*. 11.99±9.23; *p*<0.0001), and were more likely to test negative for both ACA and ATA antibodies (37.3% *vs*. 17.1%; *p*<0.0001). Additionally, Egyptians more frequently had mRSS >14 (67.8% *vs*. 2.7%; *p*<0.0001), PAPs >35 mmHg estimated by echocardiography (34.5% *vs*. 10.5%; *p*<0.0001), past/current history of ulcers (91.7% *vs*. 43.6%; *p*<0.0001), EScSG (active disease) (41.7% *vs*. 5.7%; *p*<0.0001) and ILD (57% *vs*. 43.5%; *p*<0.025). Lastly, the severity score was higher in Egyptians, and when patients were categorised according to Medsger severity scale, we observed significant differences between the same category of the two cohorts (Table III). The comparison of drug therapies of the lcSSc form in Egyptian and Italian patients was also recorded (Table IV).

Regarding the dcSSc form, Egyptian patients were significantly younger (41.71±11.69 *vs*. 56.34±11.96; *p*<0.0001), had a shorter disease duration (7.38±7.10 *vs*. 11.52±8.011; *p*<0.003), and had a higher mRSS>14 (97.3% *vs*. 28.8%; *p*<0.0001), PAPs >35 mmHg estimated by echocardiography (42.1% *vs*. 10%; *p*<0.0001), past/current history of ulcers (98.7% *vs*. 76.2%; *p*<0.0001); EScSG (active disease) (71.4% *vs*. 34%; *p*<0.0001); ILD (71.4% *vs*. 34%; *p*<0.0001). Furthermore, the severity score was higher in dcSSc Egyptian patients than in Italians, and when patients were categorised according to Medsger severity scale, we observed significant differences between the same category of the two cohorts (Table III). The comparison of drug therapies of the dcSSc form in Egyptians and Italians was also recorded (Table IV).

Table III. Comparison of severity score of the LcSSc and DcSSc form in Egyptian and Italian patients.

	All LcSSc			All DcSSc		
Severity score, n (%)	Egyptian	Italian	*p*-value	Egyptian	Italian	*p*-value
General						
0 (normal)	31 (26.3)	168 (84)	**<0.0001**	17 (22.7)	47 (85.5)	**<0.0001**
1 (mild)	60 (50.8)	29 (14.5)	**<0.0001**	38 (50.7)	6 (10.9)	**<0.0001**
2 (moderate)	27 (22.9)	2 (1)	**<0.0001**	17 (22.7)	2 (3.6)	**<0.002**
3 (severe)	0 (0)	1 (0.5)	0.442	3 (4)	0 (0)	0.133
4 (end stage)	-	-	-	-	-	-
Peripheral vascular						
0 (normal)	13 (10.7)	20 (10)	0.851	2 (2.6)	2 (3.6)	0.741
1 (mild)	33 (27)	120 (60)	**<0.0001**	10 (13.2)	25 (45.5)	**<0.0001**
2 (moderate)	31 (25.4)	42 (21)	0.359	13 (17.1)	20 (36.4)	**<0.012**
3 (severe)	45 (36.9)	18 (9)	**<0.0001**	51 (67.1)	8 (14.5)	**<0.0001**
4 (end stage)	-	-	-	-	-	-
Skin						
0 (normal)	10 (8.2)	99 (50)	**<0.0001**	1 (1.3)	12 (22.2)	**<0.0001**
1 (mild)	40 (32.8)	95 (48)	**<0.008**	8 (10.5)	37 (68.5)	**<0.0001**
2 (moderate)	6 (51.6)	4 (2)	**<0.0001**	27 (35.5)	5 (9.3)	**<0.001**
3 (severe)	9 (7.4)	0 (0)	**<0.0001**	30 (39.5)	0 (0)	**<0.0001**
4 (end stage)	-	-	-	10 (13.2)	0 (0)	**<0.006**
Joint/tendon						
0 (normal)	62 (51.2)	167 (83.5)	**<0.0001**	23 (30.3)	36 (65.5)	**<0.0001**
1 (mild)	39 (32.2)	17 (8.5)	**<0.0001**	30 (39.5)	8 (14.5)	**<0.002**
2 (moderate)	17 (14)	12 (6)	**<0.015**	22 (28.9)	4 (7.3)	**<0.002**
3 (severe)	3 (2.5)	3 (1.5)	0.530	1 (1.3)	2 (3.6)	0.381
4 (end stage)	0 (0)	1 (0.5)	0.436	0 (0)	5 (9.1)	**<0.007**
Muscles						
0 (normal)	58 (47.5)	195 (98)	**<0.0001**	27 (35.5)	48 (87.3)	**<0.0001**
1 (mild)	53 (43.4)	3 (1.5)	**<0.0001**	42 (55.3)	5 (9.1)	**<0.0001**
2 (moderate)	11 (9)	1 (0.5)	**<0.0001**	5 (6.6)	1 (1.8)	0.198
3 (severe)	-	-	-	2 (2.6)	0 (0)	0.225
4 (end stage)	-	-	-	0 (0)	1 (1.8)	0.238
GI tract						
0 (normal)	30 (24.6)	106 (54.9)	**<0.0001**	16 (21.1)	25 (46.3)	**<0.002**
1 (mild)	60 (49)	82 (42.5)	0.245	32 (42.1)	25 (46.3)	0.635
2 (moderate)	30 (24.6)	5 (2.6)	**<0.0001**	24 (31.6)	2 (3.7)	**<0.0001**
3 (severe)	2 (1.6)	0 (0)	0.074	0 (0)	1 (1.9)	0.234
4 (end stage)	-	-	-	4 (5.3)	1 (1.9)	0.319
Lung						
0 (normal)	66 (54.1)	162 (82.7)	**<0.0001**	36 (47.4)	42 (76.4)	**<0.001**
1 (mild)	39 (32)	27 (13.8)	**<0.0001**	32 (42.1)	13 (23.6)	0.028
2 (moderate)	15 (12.3)	6 (3.1)	**<0.001**	8 (10.5)	0 (0)	**<0.013**
3 (severe)	2 (1.6)	1 (0.5)	0.311	-	-	-
4 (end stage)	-	-	-	-	-	-
Heart						
0 (normal)	27 (22.1)	82 (42.3)	**<0.0001**	14 (18.4)	13 (23.6)	0.466
1 (mild)	50 (41)	44 (22.7)	**<0.001**	32 (42.1)	15 (27.3)	0.081
2 (moderate)	38 (31.1)	49 (25.3)	0.254	19 (25)	17 (30.9)	0.455
3 (severe)	7 (5.7)	18 (9.3)	0.256	11 (14.5)	9 (16.4)	0.767
4 (end stage)	0 (0)	1 (0.5)	0.427	0 (0)	1 (1.8)	0.238
Kidney						
0 (normal)	109 (89.3)	193 (96.5)	**<0.010**	64 (84.2)	54 (98.2)	**<0.008**
1 (mild)	7 (5.7)	5 (2.5)	0.137	5 (6.6)	1 (1.8)	0.198
2 (moderate)	3 (2.5)	1 (0.5)	0.124	5 (6.6)	0 (0)	0.052
3 (severe)	3 (2.5)	0 (0)	0.026	2 (2.6)	0 (0)	0.225
4 (end stage)	0 (0)	1 (0.5)	0.434	-	-	-

lcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis.

Discussion

Our study highlights the differences in demographic, clinical, serological features, and treatments between two independent cohorts of SSc patients, Egyptians and Italians. These two geographically proximate Mediterranean cohorts representing culturally different populations, exhibit distinct genetic backgrounds, with the Egyptian cohort reflecting an African ancestry and the Italian cohort representing a Caucasian lineage. This comparison provides insight into how genetic, environmental, and regional factors may influence SSc disease presentation and management. In fact, an analysis of SSc clinical presentation across EUSTAR centres in Europe revealed significant geographical variability with Eastern European centres managing patients with more

Table IV. Comparison of drug therapies of the LcSSc and DcSSc form in Egyptian and Italian patients.

	All LcSSc			All DcSSc		
Drug, n (%)	Egyptian	Italian	*p*-value	Egyptian	Italian	*p*-value
sDMARDs	113 (94.2)	67 (37.2)	**<0.0001**	72 (94.7)	26 (48.1)	**<0.0001**
Cyclophosphamide	14 (11.7)	0 (0)	**<0.0001**	4 (5.3)	3 (5.6)	0.942
Mycophenolate	19 (15.8)	33 (17.3)	0.740	8 (10.5)	13 (24.1)	**<0.039**
Azathioprine	18 (15)	11 (5.8)	**<0.006**	14 (18.4)	5 (9.3)	0.145
Methotrexate	61 (50.8)	13 (6.8)	**<0.0001**	44 (57.9)	3 (5.6)	**<0.0001**
Hydroxychloroquine	32 (26.7)	11 (5.8)	**<0.0001**	15 (19.7)	5 (9.3)	0.103
Glucocorticoids	43 (35.8)	90 (47.1)	0.050	22 (28.9)	25 (53.2)	**<0.042**
bDMARDs	0 (0)	1 (0.5)	0.427	0 (0)	2 (3.7)	0.091
Rituximab	0 (0)	1 (0.5)	0.425	0 (0)	1 (1.9)	0.234
Tocilizumab	0 (0)	0 (0)	-	0 (0)	1 (1.9)	0.234
Calcium channels blockers	103 (85.8)	149 (78)	0.087	70 (92.1)	46 (85.2)	0.210
Phosphodiesterase-5 inhibitors	16 (13.3)	3 (1.6)	**<0.0001**	7 (9.2)	0 (0)	**<0.022**
Anti-endothelin antagonists	0 (0)	15 (7.9)	**<0.002**	0 (0)	12 (22.2)	**<0.0001**
Prostacyclin analogues	0 (0)	55 (28.8)	**<0.0001**	0 (0)	29 (53.7)	**<0.0001**
Antiaggregants	0 (0)	167 (87.4)	**<0.0001**	0 (0)	46 (85.2)	**<0.0001**
Anticoagulants	0 (0)	4 (2.1)	0.111	-	-	-
ACE inhibitors	37 (30.8)	72 (37.7)	0.217	22 (28.9)	21 (38.9)	0.235
Proton pump inhibitors	57 (47.5)	176 (94.1)	**<0.0001**	40 (52.6)	52 (96.3)	**<0.0001**

sDMARDs: synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biologic disease-modifying anti-rheumatic drugs; ACE: angiotensin converting enzyme.

severe disease phenotypes compared to other regions (27).

In both cohorts, females were more than 90%. Egyptians had a more severe disease than Italians, as assessed by Medsger's severity score. In particular, Egyptians showed a younger age, an earlier onset of the first non-RP symptom, and a more severe lung and cutaneous involvement. Egyptians also exhibited a higher percentage of the active form of the disease and increased sPAP estimated by echocardiography, than Italians. Regarding autoantibodies, most patients from both cohorts were positive for ANA. Italians had a higher frequency of ATA or ACA antibodies, while Egyptians were more likely to be negative for both ACA and ATA. Lastly, Egyptians had higher rates of sDMARDs usage, except for MMF. Most Italians, unlike Egyptians, were under treatment with vasoactive therapy. Notably, Egyptians with the lcSSc showed a more severe clinical phenotype and course, than their Italian counterparts with the same disease form.

The Egyptians exhibited a younger age at disease onset and had less disease duration from the occurrence of non-RP symptoms compared to Italians (Table I). This demographic distribution agrees with previous smaller studies (18, 29-32). Our data align with other studies enrolling Italian SSc patients confirming a higher mean age at disease onset and duration (28-31). This finding may suggest that the more severe SSc-associated symptoms may contribute to an early diagnosis of the disease in Egyptians while a mild clinical phenotype could contribute to a delayed diagnosis in Italians.

Regarding immunological findings, differences in the autoantibodies profile have also been reported between races (32). We observed that the prevalence of ATA was higher in Italians than in Egyptians. This condition could not be fully explained considering the more severe disease of Egyptians and the increased number of patients with the dcSSc of the disease. Furthermore, Egyptians were more likely to be negative for both ACA and ATA antibodies than Italians. It has been reported that some small cohorts of SSc patients showed that ACA was more frequent than ATA (33). One study showed that the absence of ACA and ATA did not preclude internal organ involvement. Double-negative patients for ACA and ATA developed a higher rate of ILD, although the prevalence and severity may vary from patient to patient (34). Moreover, novel SSc-specific autoantibodies have been described in about 10% of 'seronegative' SSc patients (35). In the future, these apparently conflicting data may be better understood by extending the autoantibodies research to other autoantibody specificities including anti-Pol III antibodies, To/Th, and others generally associated with more severe disease.

Regarding the clinical presentation of the disease, we showed that Egyptians had more frequent lung involvement than Italians, with 50% affected compared to 20% of Italians. Furthermore, almost 75% of Italians had mild lung involvement, by Medsger's severity score, compared to 36% of Egyptians. Twelve % out of Egyptians had moderate-severe lung involvement compared to 3.5% out of Italians. No severe lung involvement was observed for the Italians when compared to 1% of Egyptians and this more severe ILD in Egyptians mirrors already published data (18, 36) with non-specific interstitial pneumonia pattern being the most observed at HRCT (37). Another study enrolling Egyptians showed that 30% of patients had mild restriction, 26% had moderate restriction, 28% had severe restriction, based on the PFTs results (18). A radiologic study enrolled 15 SSc patients showed that 53.3% of patients had mild ILD, 26.7% had moderate ILD and 20% had severe ILD, according to ILD scoring system (38). Finally, ILD was signif-

icantly more frequent within the dcSSc compared to the lcSSc form in Egyptians (39). In Egyptians and Italians, ILD was significantly associated with higher skin scores, cardiac involvement, ATA positivity, and late capillaroscopic pattern.

PAH is a serious SSc complication and a leading cause of death. Patients with estimated sPAP>35mmHg are at higher risk of presenting PH with the majority of SSc PAH studies using sPAP as a suitable parameter for patients screening (24). We showed that sPAP>35mmHg, by echocardiography, was more frequent in Egyptians than in Italians (Table I). Several studies in small Egyptian cohorts suggested a percentage of less than 20% of PH by indirect methods (echocardiography and HRCT) (18,40). The first single-centre registry for PH in Egypt showed that idiopathic PAH is the most common cause of PAH in Egypt. Among patients with PAH associated with connective tissue diseases, it has been shown that those patients have delayed referrals, leading to poor survival (41). However, we may only speculate about the real incidence of PAH in the Egyptian cohorts, lacking these patients the results of the gold standard assessment (RHC). In different studies assessing the prevalence of PH in SSc Italian patients, the results ranged from 6.5% to 14% as showed by RHC (42, 24).

Egyptians exhibited more severe skin involvement than Italians, with nearly 80% having a mRSS>14, despite the more frequent administration of drugs such as cyclophosphamide (43), and MMF (44). Disease onset and severity may be influenced by genetic, epigenetic, and environmental factors (45). Indeed, a study on 63 Egyptian SSc patients and 35 controls, investigating the circulating expression profiles of 4 skin-related long non-coding RNAs showed a strong correlation with the clinical and immunological SSc features (46). B-cell activating factor, a cytokine involved in B-cell maturation and survival and implicated in fibrosis and autoimmunity, is present at elevated levels in SSc patients, including Egyptians (47-49). Lastly, environmental factors (pollutants, chemical or physical agents, climatic factors, working activities, infectious stimuli, environmental temperature, diet, geographic area, drugs) may cause an immune system dysregulation in genetically predisposed subjects as confirmed by the development of SSc in silica-exposed subjects (50-52).

Ischaemic digital ulcers were more frequent in Egyptians than Italians, likely because Egyptians tended not to treat RP with prostacyclin analogues which are effective in the healing of ischaemic digital ulcers, and with anti-endothelin drug that prevents new ulcer formation in 30% of patients (53). Furthermore, in a case-control study of 140 Egyptian SSc patients, endothelial vinculin overexpression may give rise to anti-vinculin antibodies, which may contribute to the development of vasculopathy and lung fibrosis (34). Moreover, Egyptian SSc patients with annexin V antibodies (annexin V exerts antithrombotic activity) had worse digital microangiopathy and a higher frequency of ILD and PAH (54, 55).

A descriptive analysis of lcSSc in both Egyptians and Italians revealed several key differences in demographic and disease-specific features. Egyptians with lcSSc were significantly younger, had a shorter disease duration, and exhibited more severe clinical manifestations, including higher mRSS, increased sPAP, more active disease, and a higher incidence of past or current history of ulcers compared to their Italian counterparts. Moreover, Egyptians were more likely to test negative for both ACA and ATA and had higher severity scores according to the Medsger severity scale. Furthermore, Egyptians with dcSSc were younger, had a shorter disease duration, and exhibited more severe clinical features, including higher mRSS, increased sPAP, more active disease, and a higher incidence of ulcers compared to Italians. Differently from lcSSc, we did not observe any significant difference between the dcSSc Egyptians and Italians regarding the frequency of the disease-specific autoantibodies and ILD.

We are aware of some limitations of this study. Firstly, the cross-sectional design may preclude the establishment of causal relationships. Secondly, the statistical power may have been influenced by the unequal distribution of patients across the 2 cohorts. Thirdly, the insufficient characterisation of all the autoantibody specificities could impact the generalisability of the findings. Fourthly, PAH was not assessed using RHC, the gold standard for diagnosis, which could have provided a more accurate and reliable measure of the condition. Lastly, given the lack of treatment randomisation, the possible association between treatments and different outcomes cannot be uniquely ascertained.

Despite these limitations, the study provides valuable insights into how genetic, environmental, and regional factors may influence SSc clinical phenotype and course, particularly when comparing geographically proximate, yet genetically distinct, populations. Furthermore, the study raises awareness of the need for considering regional and genetic factors in clinical practice, suggesting a tailored approach to disease management for diverse patient populations.

In conclusion, this study analysed the demographic, clinical, and serologic variation in Egyptian and Italian patients, showing several differences to be further investigated in adequately powered studies.

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