Racial differences in systemic sclerosis disease presentation: a European Scleroderma Trials and Research group study

Veronika K. Jaeger [1], Mohammed Tikly[2], Dong Xu[3], Elise Siegert[4], Eric Hachulla[5], Paolo Airò[6], Gabriele Valentini[7], Marco Matucci Cerinic[8], Oliver Distler[9], Franco Cozzi[10], Patricia Carreira[11], Yannick Allanore[12], Ulf Müller-Ladner[13], Lidia P. Ananieva[14], Alexandra Balbir-Gurman[15], Jörg H. W. Distler[16], Laszlo Czirják[17], Mengtao Li[3], Jörg Henes[18], Sergio A. Jimenez [19], Vanessa Smith [20], Nemanja Damjanov[21], Christopher P. Denton [22], Francesco DelGaldo[23], Lesley Ann Saketkoo[24] and Ulrich A. Walker[1]; and EUSTAR co-authors

Abstract

Objectives. Racial factors play a significant role in SSc. We evaluated differences in SSc presentations between white patients (WP), Asian patients (AP) and black patients (BP) and analysed the effects of geographical locations.

Methods. SSc characteristics of patients from the EUSTAR cohort were cross-sectionally compared across racial groups using survival and multiple logistic regression analyses.

Results. The study included 9162 WP, 341 AP and 181 BP. AP developed the first non-RP feature faster than WP but slower than BP. AP were less frequently anti-centromere (ACA; odds ratio (OR) = 0.4, $P < 0.001$) and more frequently anti-topoisomerase-I autoantibodies (ATA) positive (OR = 1.2, $P = 0.068$), while BP were less likely to be ACA and ATA positive than were WP [OR(ACA) = 0.3, $P < 0.001$; OR(ATA) = 0.5, $P = 0.020$]. AP had less often (OR = 0.7, $P = 0.06$) and BP more often (OR = 2.7, $P < 0.001$) diffuse skin involvement than had WP.

AP and BP were more likely to have pulmonary hypertension [OR(AP) = 2.6, $P < 0.001$; OR(BP) = 2.7, $P = 0.03$ *vs* WP] and a reduced forced vital capacity [OR(AP) = 2.5, $P < 0.001$; OR(BP) = 2.4, $P < 0.004$] than were WP. AP more often had an impaired diffusing capacity of the lung than had BP and WP [OR(AP *vs* BP) = 1.9, $P = 0.038$; OR(AP *vs* WP) = 2.4, $P < 0.001$]. After RP onset, AP and BP had a higher hazard to die than had WP [hazard ratio (HR) (AP) = 1.6, $P = 0.011$; HR(BP) = 2.1, $P < 0.001$].

Conclusion. Compared with WP, and mostly independent of geographical location, AP have a faster and earlier disease onset with high prevalences of ATA, pulmonary hypertension and forced vital capacity impairment and higher mortality. BP had the fastest disease onset, a high prevalence of diffuse skin involvement and nominally the highest mortality.

[1]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [2]Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa, [3]Department of Rheumatology, Peking Union Medical College Hospital, Beijing, China, [4]Department of Rheumatology and Immunology, University Hospital Charité, Berlin, Germany, [5]Département de Médecine Interne et Immunologie Clinique, Centre de Référence des Maladies Systémiques et Auto-Immunes Rares du Nord et Nord-Ouest (CERAINO), LIRIC, INSERM, Univ. Lille, CHU Lille, Lille, France, [6]UO Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italy; [7]Rheumatology Department, Second University of Naples, Naples, Italy, [8]Department of Experimental and Clinical Rheumatology, Division of Rheumatology AOUC, University of Florence, Florence, Italy, [9]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [10]Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy, [11]Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain, [12]Department of Rheumatology A, Paris Descartes University, Cochin Hospital, Paris, France, [13]Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Germany, Bad Nauheim, [14]VA Nasonova Institute of Rheumatology, Moscow, Russian Federation, [15]B. Shine Rheumatology Institute, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion – Institute of Technology, Haifa, Israel, [16]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [17]Department of Rheumatology and Immunology, University of Pécs, Pécs, Hungary, [18]Department of Internal Medicine II, Eberhard-Karls-University Tübingen, Tübingen, Germany, [19]Scleroderma Centre, Thomas Jefferson University, Philadelphia, PA, USA, [20]Faculty of Internal Medicine, Ghent University, Ghent, Belgium, [21]Institute of Rheumatology, University of Belgrade Medical School, Belgrade, Serbia, [22]Department of Rheumatology, University College London, Royal Free Hospital, London, UK, [23]Leeds Musculoskeletal Biomedical Research Unit (LMBRU), University of Leeds, Leeds, UK and [24]Tulane University Lung Centre, University Medical Centre Scleroderma and Sarcoidosis Patient Care and Research Centre, New Orleans, LA, USA

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Correspondence to: Ulrich A. Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. E-mail: ulrich.walker@usb.ch

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Rheumatology key messages

- Asian SSc-patients developed the first non-RP-feature faster than white but slower than black patients.
- Asian patients were less frequently anti-centromere and more frequently anti-topoisomerase-I-autoantibodies positive.
- After RP onset, Asian/black SSc-patients had a higher hazard to die than white SSc patients.

Introduction

Differences in the development of *Homo sapiens* across continents probably occurred in response to local environmental pressures giving rise to various populations [1]. These groups vary in genetics factors that influence immune responses and also in socioeconomic and cultural domains that may modulate the manifestation of autoimmune diseases, such as SSc [1]. The prevalence and clinical manifestations of SSc indeed vary among different racial groups [2, 3].

Studies of multi-racial cohorts including mostly African Americans, Hispanics and European descendants suggest that non-European descendants are more likely to have a more severe disease [4–6]. African Americans, for example, are known to have a higher incidence of SSc, an earlier age of onset and a greater frequency of interstitial lung disease (ILD) and pulmonary hypertension (PH) compared with white SSc patients [4, 5, 7–9]. Data on black SSc patients, however, mostly stem from African Americans and may be influenced by environmental and socioeconomic factors, and access to health care [10, 11]. Differences in the autoantibody profile have also been reported between races; ACA are frequent in Caucasian patients, whereas anti-topoisomerase-I autoantibodies (ATA) are highly prevalent in Choctaw Native Americans, Thais and African Americans [1, 3, 12, 13]. Detailed cohort studies on SSc disease presentations in Asian patients (AP) are scarce, predominantly of limited sample size, or lack comparator groups [12, 14–18]. A detailed understanding of the effects of the racial background of SSc patients has not only important implications for the appropriate monitoring, treatment and prognostication of patients, but also for a better understanding of the disease pathogenesis.

In this analysis of the multiracial, multinational database of the European Scleroderma Trials and Research group (EUSTAR) [19, 20], we aimed to investigate the effect of the patients' race on SSc presentation and to simultaneously compare disease presentations of black patients (BP) living in and outside sub-Saharan Africa, and AP living within and outside Asia.

Methods

Study population

This study is based on the multinational, longitudinal EUSTAR database. The structure of and the core data collected within the EUSTAR database have been previously described [19, 20]. Additional to disease characteristics, the self-reported racial background of the patients, i.e. white/black/Asian is also collected in the EUSTAR database. Each centre obtained local ethical committee approval, and each patient provided written informed consent prior to EUSTAR enrolment. EUSTAR data collection started in 2004 and data for this study were exported in January 2018.

Adult SSc patients were included at the baseline visit, if they fulfilled the 1980 ACR or 2013 ACR/EULAR criteria for SSc [21, 22] and if information on the patients' racial background (white patients (WP)/AP/BP) was available. Patients who self-reported as being of mixed race, i.e. white/Asian or white/black were adjudicated to the AP or BP group.

To capture a possible contribution of geographic, environmental or health care system to the SSc presentation, we compared patient groups in four ways. We first compared all WP *vs* all AP *vs* all BP in EUSTAR. Second, we used a centre-matched approach in order to reduce the possible effects of environmental factors and health care systems. In this approach, we compared AP treated outside Asia with all WP in the same centres and BP treated outside sub-Saharan Africa with all WP in the same centres.

In a third 'individual-matched' approach, we matched patients with different races for demographic features, serological features and disease subsets. Specifically, the patients were 1:1 matched according to prognostic factors such as age (±5 years), sex, time since the onset of RP (±3 years), time since the first non-RP manifestation (±3 years) and diffuse/limited presentations (except for the mRSS analyses). With this approach, we attempted to make the populations under study more similar for important prognostic factors in order to study differences between races independent of a referral bias to the EUSTAR centres.

Fourth, we compared AP treated within Asia *vs* AP treated outside Asia, and BP treated within sub-Saharan Africa *vs* BP treated outside sub-Saharan Africa in order to identify environmental factors contributing to SSc presentation within races.

Study outcomes

Several disease parameters were assessed: speed of SSc onset, i.e. time from RP onset to the first non-RP manifestation, forced vital capacity (FVC; % of predicted) and FVC $< 80\%$ of predicted as a proxy for a pulmonary

restrictive defect, single−breath diffusing capacity for carbon monoxide (DLCO/sb; % of predicted) and DLCO/sb < 80% of predicted, systolic pulmonary arterial pressure as estimated by echocardiography (PAPsys; mmHg) and PAPsys > 40 mmHg as a proxy for suspected PH, modified Rodnan skin thickness score (mRSS), the extent of skin involvement, i.e. diffuse/limited, autoantibody status and mortality.

Statistical analysis

Frequencies/percentages or means/standard deviations (S.D.) were calculated; demographic and disease characteristics between racial groups were compared using the χ^2-test/Fisher's exact test or ANOVA/Kruskal–Wallis test. Multiple linear and logistic regression analyses were applied allowing for clustering on the study centre level to adjust outcome/exposure associations with *a priori* defined potential confounding factors (age, sex, time since RP and since first non-RP manifestation, antibody status and diffuse/limited disease).

The speed of disease onset and the time to death were assessed by Kaplan–Meier methods and compared between the racial groups using a log-rank test. Cox-proportional hazard regression was used to adjust for potentially confounding factors, i.e. age, sex, antibody status and diffuse/limited disease. For those patients in whom the non-RP complication manifested before RP onset, the date of the first non-RP manifestation was set as 1 day after the RP onset for the above analyses.

Missing values were imputed using multiple imputation with chained equations ($m = 50$); continuous data were modelled using predictive mean matching, and categorical data were modelled by logistic regression in the imputation model [23–25]. All regression results in this paper are based on the imputed data, and all analyses were performed with Stata/IC 15.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

By January 2018, 13 377 SSc patients had been followed in the EUSTAR database. Of those, 9161 were WP, 341 AP (of which four regarded themselves as being of mixed race, i.e. AP/WP) and 198 BP (six BP/WP), and were included in this analysis. Of the AP, 208 were recruited within Asia (EUSTAR centre Beijing, China) and 133 in 34 EUSTAR centres outside Asia; 124 patients were followed by European centres, four patients by a US centre and one patient by a centre in South Africa. Of the BP, 82 were recruited within Africa (EUSTAR centre Johannesburg) and 116 in 35 centres outside Africa of which 33 patients were from nine centres in the Americas and 83 patients were from 26 centres in Europe.

In the centre-matched analyses, the 133 AP from outside Asia were compared with 4700 WP being followed in the same centres as the AP. The 116 BP followed outside Africa were compared with 3824 WP followed in the same centres. In the individual-matched analyses, 337 AP were matched to 337 WP and 197 BP were matched to 197 WP.

On average, AP and BP were 10 years younger than WP ($P < 0.001$, Table 1). Of the WP, more were male (16%) than were the AP or BP (11% and 13%, respectively; Table 1).

Autoantibodies

Comparing all AP with all WP, AP were less likely to be ACA positive [odds ratio (OR) = 0.4, 95% CI: 0.3, 0.5, $P < 0.001$] and with a trend to be ATA positive (OR = 1.2, 95% CI: 1.0, 1.6, $P = 0.068$). The same pattern was seen in the centre-matched and individual-matched analyses (Tables 2 and 3). AP treated within Asia were comparably often ACA and ATA positive than AP treated outside Asia [OR(ACA) = 0.7, 95% CI: 0.3, 1.4, $P = 0.31$; OR(ATA) = 0.9, 95% CI: 0.6, 1.4, $P = 0.62$].

BP were less likely to be ACA and ATA positive than were all WP and individual-matched WP [OR(ACA) = 0.3, 95% CI: 0.2, 0.5, $P < 0.001$; OR(ATA) = 0.5, 95% CI: 0.3, 0.9, $P = 0.020$; Table 3]. In the centre-matched analysis, BP were also less likely to harbour ACA, but similarly likely to be ATA positive than were the centre-matched WP (Table 2). BP from the Johannesburg centre were equally likely to be ACA positive as BP from outside sub-Saharan Africa (OR = 0.7, 95% CI: 0.2, 2.0, $P = 0.50$). However, they were less likely to be ATA positive (OR = 0.4, 95% CI: 0.2, 0.8, $P = 0.009$).

To sum up, AP harbour substantially less ACA and slightly more ATA than WP, while BP are less often ACA positive than WP.

Speed of disease onset

AP and BP developed RP at a younger age than did WP (Table 1). After RP onset, BP evolved the first non-RP feature faster than AP and WP (Table 1; Fig. 1A). Two years after RP onset, 66% of WP (95% CI: 65%, 67%) had experienced their first non-RP SSc manifestation, compared with 74% of AP (95% CI: 69%, 79%) and 87% of BP (95% CI: 82%, 92%). These kinetics of a faster disease onset in BP and AP were also seen after adjustment for potentially confounding factors [hazard ratio (HR) (BP) = 1.4, 95% CI: 1.2, 1.5, $P < 0.001$; HR(AP) = 1.1, 95% CI: 1.0, 1.2, $P = 0.009$; both *vs* WP; HR(BP *vs* AP) = 1.2, 95% CI: 1.0, 1.4, $P = 0.013$].

Restricting the study population to the centre-matched populations, there was still a significant difference in the speed of disease onset between BP and WP (HR(BP) = 1.3, 95% CI: 1.1, 1.5, $P = 0.001$). Similarly, AP evolved with their first non-RP manifestation slightly faster than did the centre-matched WP, even though this difference was only numerical (HR(AP) = 1.1, 95% CI: 0.9, 1.3, $P = 0.36$).

There were, however, no differences in time to the first non-RP feature between AP treated outside Asia and those treated within Asia (Fig. 1B) and between BP treated outside and those treated within sub-Saharan Africa (Fig. 1C).

Table 1 Demographic and disease characteristics by race

Characteristic	*n*[a]	White patients	Asian patients	Black patients	*P*-value
N	9700	9161	341	198	
Age, mean (S.D.), years	9698	56.7 (13.8)	46.3 (12.6)	45.6 (11.8)	<0.001
Age at RP onset, mean (S.D.), years	9446	44.2 (15.4)	38.1 (13.3)	37.8 (12.2)	<0.001
Male sex, %	9700	16.0	11.4	13.1	0.047
Disease characteristics					
Time since RP onset, median (IQR), years	9447	9.2 (3.8–17.7)	5.2 (2.1–11.0)	5.9 (2.0–10.9)	<0.001
Time since first non-RP manifestation, median (IQR), years	8683	6.5 (2.7–12.9)	4.1 (1.5–9.0)	5.4 (2.1–10.4)	<0.001
Time RP to non-RP, median (IQR), years	8560	0.4 (0–4.0)	0 (0–2.0)	0 (0–0.4)	<0.001
mRSS, mean (S.D.)	8804	8.8 (8.1)	8.0 (7.7)	11.5 (10.4)	<0.001
Cutaneous involvement, %	9628				<0.001
Sine		10.0	5.0	7.7	
Limited		64.4	67.2	35.9	
Diffuse		25.6	27.9	56.4	
Oesophageal symptoms, %	9604	62.5	55.0	58.7	0.013
Stomach symptoms, %	9534	21.5	22.2	23.2	0.81
Intestinal symptoms, %	9552	24.9	25.1	28.9	0.44
Puffy fingers, ever, %	8552	51.1	77.8	36.5	<0.001
Digital ulcers, ever, %	9460	37.1	27.7	42.6	0.001
Telangiectasia, %	3498	59.2	44.3	18.0	<0.001
LVEF, median (IQR), %	6582	61 (60–66)	68 (63–70)	60 (58–65)	<0.001
LVEF <50%, %					
PAPsys, mean (S.D.), mmHg	6017	29 (15)	34 (17)	31 (16)	<0.001
PAPsys >40 mmHg, %		11.6	17.9	16.7	0.004
DLCO/sb, mean (S.D.), % of predicted	7397	69 (22)	61 (18)	66 (24)	<0.001
DLCO/sb <80% of predicted, %		70.2	83.8	73.6	<0.001
FVC, mean (S.D.), % of predicted	7291	95 (22)	82 (18)	81 (25)	<0.001
FVC <80% of predicted, %		22.9	43.8	50.4	<0.001
Renal crisis, %	9565	2.0	2.4	0.5	0.30
Laboratory parameters					
ANA positive, %	9463	96.3	97.6	94.8	0.26
ACA positive, %	8917	41.6	16.4	10.4	<0.001
ATA positive, %	8953	35.3	46.5	34.1	<0.001
RNAP-III positive, %	4718	4.7	8.3	6.7	0.26
Hypocomplementaemia, %	6856	7.6	8.1	2.0	0.10
Proteinuria, %	8579	5.5	7.8	8.2	0.076

[a]Number of patients with available information for each variable. ATA, anti-topoisomerase autoantibodies; DLCO/sb, single breath diffusing capacity for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York heart association; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography; RNAP-III, anti-RNA polymerase-III autoantibodies.

To sum up, BP developed RP at a younger age than WP and AP. In terms of evolution with their first non-RP SSc feature, BP were also fastest, followed by AP and WP. The speed of disease evolution was independent of centre location.

Skin involvement

The prevalence of diffuse skin involvement was similar between AP and WP, but higher in BP (Table 1). In multivariable analysis, AP had diffuse skin involvement less often than had WP (OR 0.7, 95% CI: 0.5, 1.0, $P = 0.06$) while BP were more likely to have diffuse disease than were WP (OR 2.7, 95% CI: 1.9, 4.0, $P < 0.001$). The same was seen when comparing diffuse skin status among AP with that of individual-matched WP (OR 0.5, 95% CI: 0.4, 0.8, $P < 0.001$). However, when comparing the patients from outside Asia with the centre-matched WP, the odds of diffuse skin involvement in AP was comparable to that in WP (OR 1.1, 95% CI: 0.7, 1.7, $P = 0.57$).

BP were more likely to have diffuse disease when compared with individual-matched WP (OR 2.3, 95% CI: 1.5, 3.6, $P < 0.001$). Similarly, BP outside sub-Saharan Africa were more often of the diffuse subset than were the centre-matched WP (OR 2.4, 95% CI: 1.5, 3.8, $P < 0.001$).

A similar pattern was apparent looking at the mRSS scores for AP and BP (Fig. 2). Multivariably, WP had a mRSS of 12, AP of 10 and BP of 14 [Fig. 2A; P(WP/AP) < 0.001; P(WP/BP) $= 0.015$; P(AP/BP) < 0.001].

To sum up, AP tend to have less severe skin sclerosis than WP, whereas BP have more severe skin involvement. The racial effect driving skin status appeared to be largely independent of geographical location.

Table 2 Multiple adjusted logistic regression results of centre-matched patients by racial status

Characteristics	Asian patients			Black patients		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Diffuse SSc	1.13	0.8, 1.7	0.57	2.38	1.5, 3.8	<0.001
FVC <80% of predicted	3.85	2.6, 5.7	<0.001	4.16	2.8, 6.3	<0.001
DLCO/sb <80% of predicted	3.10	1.7, 5.5	<0.001	1.97	1.2, 3.3	0.010
PAPsys >40 mmHg	1.35	0.6, 3.0	0.46	2.57	1.3, 5.0	0.006
ACA positive	0.45	0.3, 0.7	0.002	0.30	0.2, 0.6	<0.001
ATA positive	1.41	0.8, 2.4	0.20	0.86	0.5, 1.5	0.58
RNAP-III positive	1.29	0.5, 3.4	0.60	0.91	0.3, 2.6	0.86

The ORs represent Asian patients followed outside Asia ($n = 133$) compared with all white patients of the EUSTAR centres in which the Asian patients were treated ($n = 4700$). The ORs of the black patients are based on the black patients followed outside sub-Saharan Africa ($n = 116$) compared with all white patients of the EUSTAR centres in which the black patients were treated ($n = 3824$). Results are adjusted for age, sex, time since the onset of RP, time since the first non-RP manifestation, autoantibody status (except for the autoantibody analysis) and the extent of skin involvement (except for the subset analysis). ATA, anti-topoisomerase autoantibodies; DLCO/sb, single breath diffusing capacity for carbon monoxide (% of predicted); FVC, forced vital capacity (% of predicted); OR, odds ratio; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography (mmHg); RNAP-III, anti-RNA-polymerase-III autoantibodies.

Table 3 Multiple adjusted logistic regression results by the racial status of the individual-matched patients

Characteristics	Asian patients			Black patients		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Diffuse SSc	0.53	0.4, 0.8	<0.001	2.3	1.5, 3.6	<0.001
FVC <80% of predicted	2.59	1.8, 3.8	<0.001	3.06	1.8, 5.2	<0.001
DLCO/sb <80% of predicted	2.53	1.7, 3.8	<0.001	1.12	0.7, 1.9	0.68
PAPsys >40 mmHg	3.33	1.7, 6.4	<0.001	3.12	1.1, 8.7	0.030
ACA positive	0.36	0.2, 0.5	<0.001	0.36	0.2, 0.6	0.001
ATA positive	1.36	1.0, 1.9	0.057	0.67	0.4, 1.0	0.063
RNAP-III positive	4.92	0.1, 252.3	0.42	1.01	0.4, 2.5	0.98

The presented ORs of the Asian patients are based on 337 Asian patients and 197 black patients compared with age, sex, time since RP onset, time since the first non-RP manifestation and the extent of skin involvement (except for the subset analysis) individual-matched white patients. Results are adjusted for autoantibody status (except for the autoantibody analysis). ATA, anti-topoisomerase autoantibodies; DLCO/sb, single breath diffusing capacity for carbon monoxide (% of predicted); FVC, forced vital capacity (% of predicted); OR, odds ratio; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography (mmHg); RNAP-III, anti-RNA-polymerase-III autoantibodies.

Pulmonary interstitial and vascular involvement

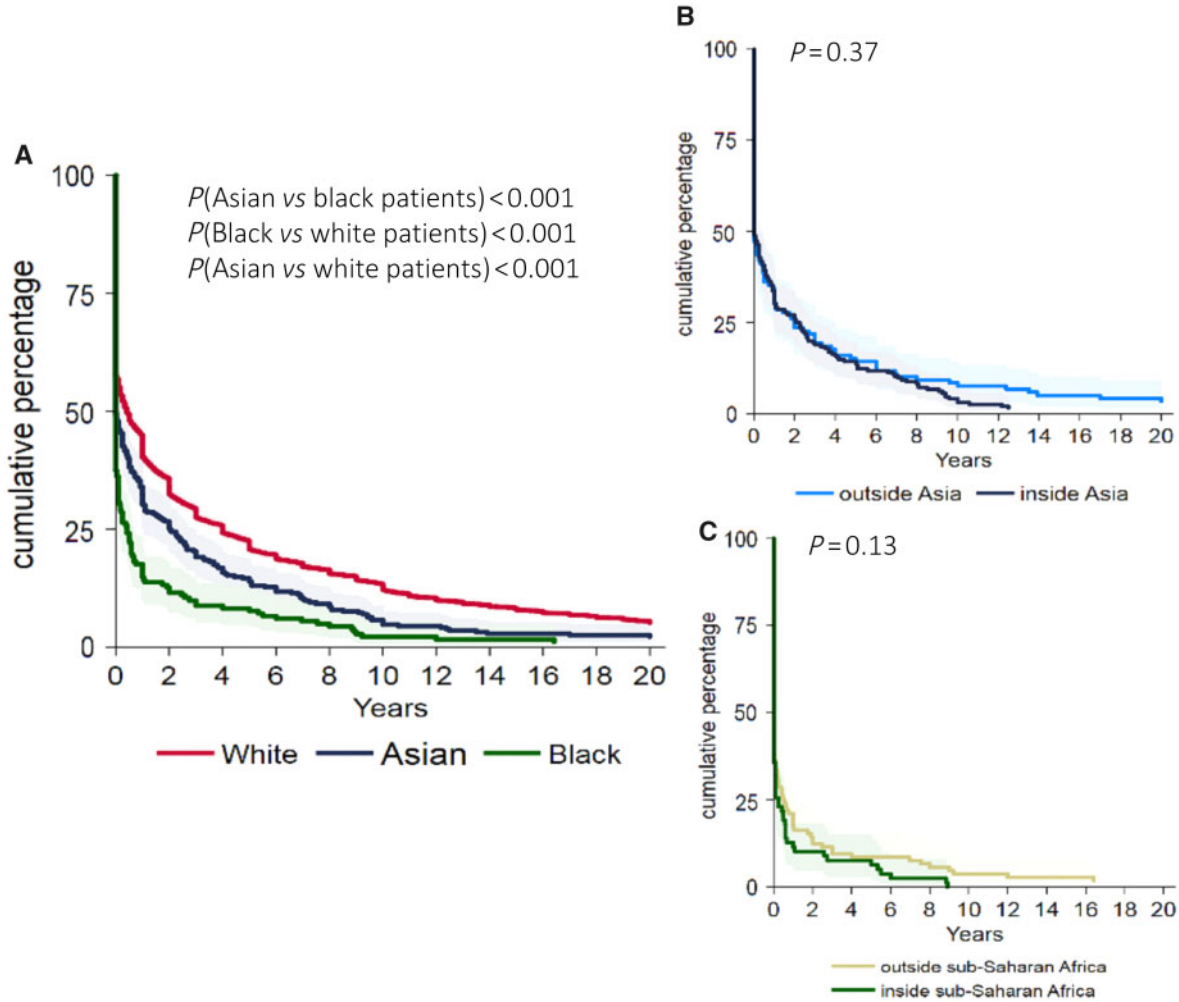
The FVC (as % of predicted) was considerably lower in AP and BP than in WP, both univariably and multivariably (Table 1; Fig. 2). AP and BP were, respectively, 2.5 times (95% CI: 1.8, 3.4, $P < 0.001$) and 2.4 times (95% CI: 1.3, 4.3, $P = 0.004$) more likely to have an FVC below 80% of predicted compared with WP. The same pattern of a lower FVC was seen comparing AP with the centre-matched WP (Fig. 2B; Table 2) and when comparing AP with the individual-matched WP (Fig. 2C; Table 3). The AP treated in the EUSTAR centre in Beijing had a comparable FVC to the AP treated outside Asia (Fig. 2D).

The FVC was lower in BP than in WP (Fig. 2A–C; Tables 2 and 3), but comparable to that in AP. Interestingly, BP treated outside sub-Saharan Africa had a considerably lower FVC than had BP followed in Johannesburg (Fig. 2D).

Overall, AP had considerably lower DLCO/sb levels than those of WP, whereas the DLCO/sb levels in BP were comparable to those of WP (Table 1; Fig. 2A). AP were more likely to have a DLCO/sb of <80% of predicted than were WP (OR = 2.4, 95% CI: 1.8, 3.3, $P < 0.001$). This was also the case when comparing AP treated outside Asia with WP of the same centres (i.e. centre-matched; Fig. 2B; Table 2) and when comparing AP with their individual-matched WP (Fig. 2C; Table 3). In accordance with the above results, AP treated within Asia had DLCO/sb levels similar to AP treated outside Asia [Fig. 2D; OR(<80% of predicted) = 0.6, 95% CI: 0.3, 1.3, $P = 0.17$].

Centre-matched (Fig. 2B; Table 2) BP had lower DLCO/sb levels than their white matched comparison group, but

Fig. 1 Kaplan–Meier curves with 95% CI of the first non-RP feature after RP onset



The Kaplan–Meier curves (**A**) by racial group, (**B**) by the geographical location of Asian patients (outside Asia or within Asia), and (**C**) by the geographical location of black patients (outside sub-Saharan Africa or within sub-Saharan Africa). Patients who experienced their first non-RP feature of the disease before the onset of RP were attributed a simultaneous onset.

individual-matched BP had comparable DLCO/sb levels to the individual-matched BP comparison group (Fig. 2C; Table 3). BP treated within sub-Saharan Africa had significantly higher DLCO/sb levels than had BP treated outside sub-Saharan Africa [Fig. 2D; OR(<80% of predicted) = 0.4, 95% CI: 0.2, 0.8, $P = 0.018$].

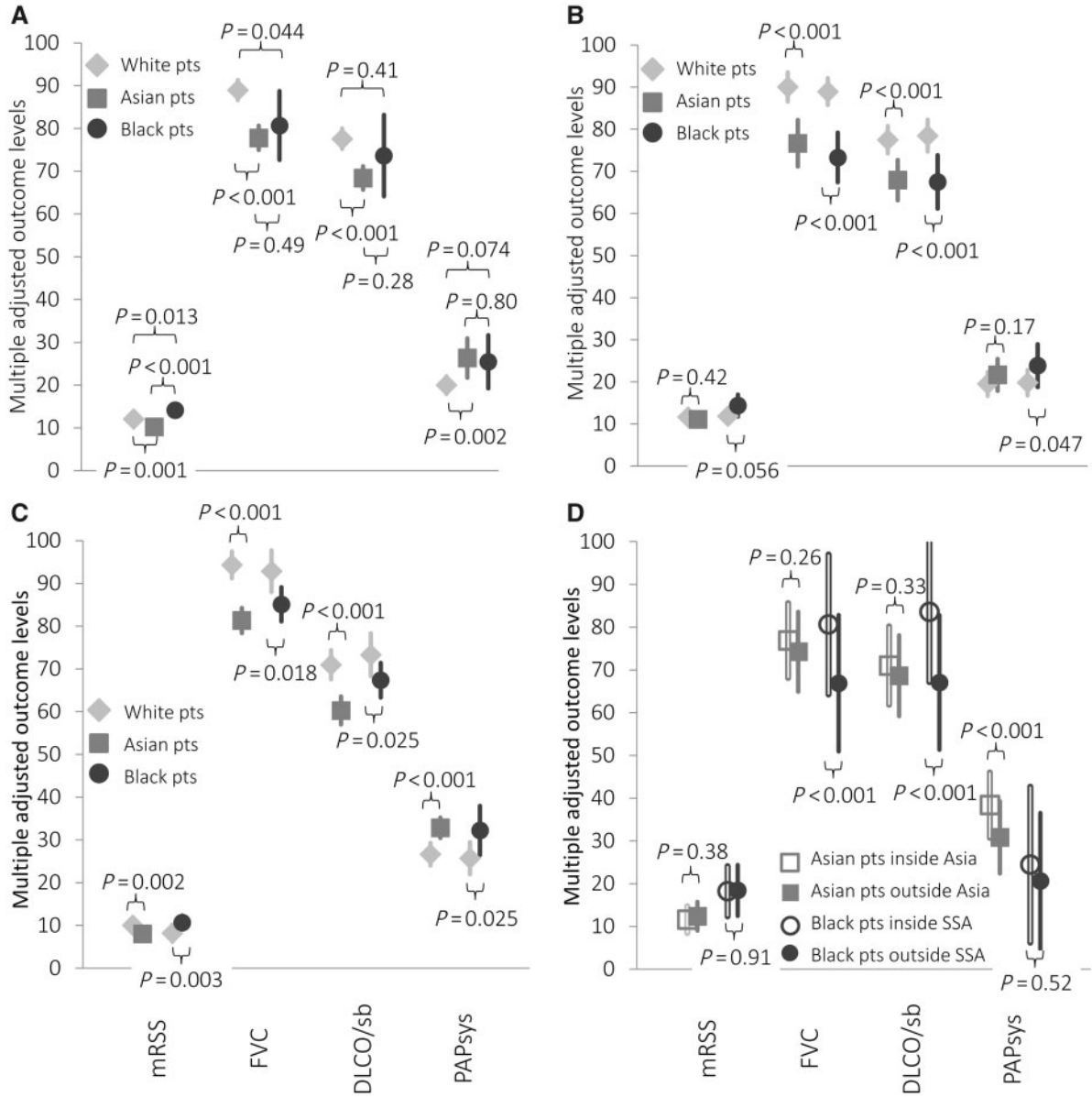
With regards to PAPsys, AP had higher levels than had WP (Table 1; Fig. 2A). PAPsys levels were similar in BP and WP (Table 1; Fig. 2A). AP had 2.6 times the odds of having a PAPsys >40 mmHg than WP (95% CI: 1.4, 4.6, $P = 0.001$). However, comparing AP being treated outside Asia with the centre-matched WP, this difference in PAPsys levels disappeared (Fig. 2B; Table 2). AP compared with their individual-matched WP had higher PAPsys levels (Fig. 2C; Table 3). AP from within Asia had significantly higher PAPsys levels than AP followed outside Asia [Fig. 2D; OR(>40 mmHg) = 3.0, 95% CI: 1.3, 7.0, $P = 0.010$].

BP treated outside sub-Saharan Africa had slightly higher PAPsys levels than had WP treated at the same centres (i.e. centre-matched; Fig. 2B; Table 2). This difference was also apparent when comparing BP with individual-matched WP (Fig. 2C; Table 3). BP from the centre Johannesburg had comparable PAPsys levels to BP treated outside sub-Saharan Africa [Fig. 2D; OR(>40 mmHg) = 1.4, 95% CI: 0.2, 8.7, $P = 0.73$].

Mortality

For the mortality part of this study, we had a median observation time (i.e. from RP onset to either death or the last time the patient was known to be alive) of 12.5 years [interquartile range (IQR) 6.5–21.4 years] in WP, 9.8 years (IQR 6.1–15.5 years) in AP and 8.6 years (IQR 3.9–14.4 years) in BP. During this time, 12% of WP, 9% of AP and 13% of BP died. Ten years after the first RP

Fig. 2 Multiple adjusted levels of the outcome measures and corresponding 95% confidence intervals by racial status



Results (**A**) of all included patients, (**B**) of the centre-matched patients, (**C**) of individual-matched patients [matched by age, sex, time since RP onset, time since the first non-RP manifestation and the extent of skin involvement (except for the mRSS analysis)] and (**D**) comparing black patients from within sub-Saharan Africa and black patients from outside sub-Saharan Africa and Asian from within Asia and Asian patients from outside Asia. Results illustrated in (**A**, **B**, **D**) are adjusted for age, sex, time since the onset or PR, time since the first non-RP manifestation, autoantibody status and the extent of skin involvement (except for the mRSS analyses). Results illustrated in (**C**) are only adjusted for autoantibody status. DLCO/sb, single breath diffusing capacity for carbon monoxide (% of predicted); FVC, forced vital capacity (% of predicted); mRSS, modified Rodnan skin score; PAPsys, systolic pulmonary artery pressure as estimated by echocardiography (mmHg), SSA, sub-Saharan Africa.

occurrence, 6.5% of WP (95% CI: 6%, 7%), 7.6% of AP (95% CI: 5%, 12%) and 10.4% of BP (95% CI: 6%, 17%) had died.

AP and BP had higher hazards to die than had WP (as measured from RP onset; HR = 1.6, 95% CI: 1.1, 2.2, $P = 0.011$; HR = 2.1, 95% CI: 1.5, 2.9, $P < 0.001$; respectively). AP and BP had a comparable hazard to die (HR = 1.3, 95% CI: 0.8, 2.0, $P = 0.23$). However, AP had a comparable hazard to die in comparison with the centre-matched WP and in comparison with the

individual-matched WP (HR = 1.1, 95% CI: 0.5, 2.2, $P = 0.80$; HR = 1.6, 95% CI: 0.8, 3.0, $P = 0.18$; respectively). AP from the centre in Beijing had a higher, but not statistically significantly higher, hazard to die (HR = 1.5, 95% CI: 0.7, 3.4, $P = 0.34$) than AP outside Asia.

BP in the centre-matched approach had a slightly higher hazard to die than the WP comparison group (HR = 1.5, 95% CI: 1.0, 2.4, $P = 0.064$). However, in the individual-matched approach, BP had a comparable hazard to die to the matched WP (HR = 1.4, 95% CI: 0.7, 2.7, $P = 0.34$) indicating that adjustment for known risk factors partly eliminated the increased mortality in BP. BP treated within sub-Saharan Africa were comparable with regards to mortality to patients treated outside sub-Saharan Africa (HR = 1.3, 95% CI: 0.5, 3.2, $P = 0.55$).

To sum up, in the EUSTAR cohort BP died faster and more frequently than WP, irrespective of geographical location. AP had also a slightly elevated mortality, which, however, partly disappeared in the matched analyses.

Discussion

In this study of >9000 white SSc patients, 341 Asian SSc patients and 198 black SSc patients, several clinical and serological differences were evident between the three racial groups. We found that BP had the fastest speed of disease onset; this, however, might have been an overestimation as RP may be less dramatic and noticeable in highly pigmented skin and hence the onset of RP might have occurred already earlier and unnoticed. AP also developed the first non-RP feature faster than WP. Compared with WP, AP had also a higher prevalence of PH and lung involvement.

The high prevalence of ATA in AP was independent of geographical location; this is in line with a Chinese study [16] and was also seen in Canada in patients of Chinese origin in comparison with European descent (47% *vs* 27%, respectively; $P = 0.02$) [17]. These findings, along with the previously discovered association of autoantibody status with HLA alleles underscore a genetic component in autoantibody predisposition [26, 27]. In the Canadian study, the high prevalence of ATA was not reflected by an increased prevalence of ILD in Chinese descendants [17, 28]. Contrasting with this, we found that AP were consistently associated, univariably, but also after accounting for autoantibody profiles, with a decreased FVC, irrespective of the treatment centre and geographical location. This finding was regardless of the analysis we applied and replicated by Asian studies that also found a high prevalence of ILD (80%) [16] and a fast evolution of lung involvement [29]. Although these differences might hint at environmental factors or differences/accessibility in the health care systems as an explanation for the ILD prevalences, our study suggests a true genetic component.

Interestingly, AP had similar proportions of limited and diffuse skin involvement compared with WP in our study. In two previous reports studying Chinese patients and a study from Thailand, however, the prevalence of diffuse skin involvement was about 50% higher than in our study [12, 16, 17]. Similar to our results, also in Thai patients, a high rate of ATA positivity was observed [12]. Additionally, Thai patients also have a high prevalence of ILD in association with ATA, but no association of ATA with diffuse skin involvement [12].

In our study, AP had higher prevalences of PH (PAPsys > 40) than had WP. This finding was not seen when comparing AP inside Asia *vs* those outside, indicating that it is independent of geographical location. Our study also indicated a higher prevalence of suspected PH in AP than in individual-matched WP. In a Chinese study including patients from the Chinese Rheumatism Data Centre, the prevalence of pulmonary arterial hypertension was similar to the prevalence of suspected PH in our study and was identified as the leading cause of death [16]. In a recent study from Canada, much higher prevalences of PH were found in patients originating from Asia (between 27% and 31%) compared with our study [30]. The authors, however, did not find a difference in PH prevalence between patients of various ethnicities [30]. This is in line with our finding that AP treated outside Asia had a similar frequency of suspected PH to that of the white centre-matched comparison group and hints towards a location-driven higher prevalence of PH in Asia.

An interesting result of our study is that AP had an increased mortality in multivariable analysis compared with WP. This finding, however, partly disappeared in the matched analyses, again being in line with the Canadian study that also found no difference in the survival time between ethnicities including WP and AP [30]. However, the compared patients were all residing in Canada. Hence, the result that AP were likely to die faster in our study is likely to be partly attributable to environmental or socioeconomic factors or differences in the health-care system. In addition, the background population mortality is different in different regions and continents, which might have also contributed to our findings.

Like most registries, the EUSTAR cohort has limitations. By design, we were unable to analyse racial differences in SSc incidence. Another limitation often arising in registries is missing data, which may lead to biased results if only patients with complete data are included [25]. We applied multiple imputation with chained equations under a missing-at-random assumption and therefore we did not exclude patients with missing data from this study [25].

It would have also been favourable to have more centres in Asia and sub-Saharan Africa included, to rule out centre-specific differences in these continents and, more importantly, to rule out country-specific differences as we only have the centre in Beijing included within Asia and the centre in Johannesburg included within sub-Saharan Africa. We can also not fully untangle the various factors associated with race including genetic and possibly behavioural factors. However, we attempted to address possible environmental confounders and differences in health-care access (e.g. referral bias) by centre-matching and individual-matching and also by comparing the patients residing within their home continents with those

living outside. Nevertheless, we had no information on how long AP and BP were residing outside their home continents. Therefore, we cannot fully decipher environmental and genetic factors on disease phenotypes also as we grouped a large variety of different ethnicities into the AP and BP categories.

In summary, this analysis is by far the largest direct comparison of different ethnicities so far; it strengthens knowledge about the clinical and serological differences between BP and WP and largely extends that on AP by suggesting that they have a relatively fast disease evolution in conjunction with high prevalences of ATA, PH and lung involvement.

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EUSTAR Collaborators (numerical order of centres): Silvia Bellando Randone, University of Florence, Italy; Bettina Bannert, University Hospital Basel, Switzerland; Florenzo Iannone, Fabio Cacciapaglia University of Bari, Italy; Britta Maurer, Suzana Jordan, Rucsandra Dobrota, Mike Becker, Carina Mihai, University of Zurich, Switzerland; Radim Becvarare, Michal Tomčík, Charles University, Prague, Czech Republic; Otylia Kowal Bielecka, Ewa Gindzienska-Sieskiewicz, Katarzyna Karaszewska, Medical University of Bialystok, Poland; Maurizio Cutolo, Carmen Pizzorni, Sabrina Paolino, Alberto Sulli, Barbara Ruaro, Elisa Alessandri, University of Genova, Italy; Antonella Riccardi, Veronica Giacco, Valentina Messitini, Rosaria Irace, Policlinico U.O. Reumatologia, Naples, Italy; Claudia Kedor, Vincent Casteleyn, Julia Hilger, Jakob Hoeppner, Charité University Hospital, Berlin, Germany; Simona Rednic, Iulia Szabo, Ana Petcu, University of Medicine & Pharmacy, 'Iuliu Hatieganu' Cluj, Cluj-Napoca, Romania; Jérome Avouac, Frantz Camelia, Carole Desbas, University Cochin Hospital, Paris, France; Panayiotis Vlachoyiannopoulos, National University of Athens, Greece; Carlo Maurizio Montecucco, Roberto Caporali, Lorenzo Cavagna, IRCCS Policlinico S Matteo, Pavia, Italy; Jiri Stork, Charles University Prague, Czech Republic; Murat Inanc, Istanbul Medical Faculty, Turkey; Beatriz E. Joven, Hospital 12 de Octubre, Madrid, Spain; Srdan Novak, Felina Anic, KBC Rijeka, Croatia; Cecilia Varju, Tunde Minier, University of Pécs, Hungary; Carlo Chizzolini, Daniela Allai, University Hospital Geneva, Switzerland; Eugene J Kucharz, Anna Kotulska, Magdalena Kopec-Medrek, Malgorzata Widuchowska, Medical University of Silesia, Katowice, Poland; Alenka Sipek Dolnicar, University Medical Centre Ljublijana, Slovenia; Bernard Coleiro, 'Stella Maris', Balzan, Malta; Armando Gabrielli, Lucia Manfredi, Devis Benfaremo, Alessia Ferrarini, University of Ancona, Italy; Dominique Farge Bancel, Adrian Hij, Pauline Lansiaux, Hôpital Saint-Louis, Paris, France; Maria Grazia Lazzaroni, Spedali Civili di Brescia, Italy; Roger Hesselstrand, Dirk Wuttge, Kristofer Andréasson, Lund University Hospital, Sweden; Duska Martinovic, Ivona Bozic, Mislav Radic, Clinical Hospital of Split, Croatia; Yolanda Braun-Moscovici, Rambam Health Care Campus, Haifa, Israel; Andrea Lo Monaco, Federica Furini, University of Ferrara, Italy; Nicolas Hunzelmann, Pia Moinzadeh, Universitätshautklinik Köln, Germany; Raffaele Pellerito, Ospedale Mauriziano, Torino, Italy; Cristian Caimmi, Eugenia Bertoldo, Università degli Studi di Verona, Italy; Jadranka Morovic-Vergles, Ivana Melanie Culo, Dubrava University Hospital, Zagreb, Croatia; Ann-Christian Pecher, Medizinische Universitätsklinik, Tübingen, Germany; Vera Ortiz Santamaria, Rheumatology Granollers General Hospital, Barcelona, Spain; Stefan Heitmann, Medeleine Codagnone, Johannes Pflugfelder, Marienhospital Stuttgart, Germany; Dorota Krasowska, Malgorzata Michalska-Jakubus, Medical University of Lublin, Poland; Matthias Seidel, Medizinische Universitäts-Poliklinik, Bonn, Germany; Paul Hasler, Samuel Kretschmar, Kantonsspital Aarau, Switzerland; Michaela Kohm, Wolfgang Goethe Universität, Frankfurt, Germany; Gianluigi Bajocchi, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Maria João Salvador, José Antonio Pereira Da Silva, Hospitais da Universidade, Coimbra, Portugal; Bojana Stamenkovic, Aleksandra Stankovic, Institute for Prevention, Treatment and Rehabilitation Rheumatic and Cardiovascular Disease Niska Banja, Serbia and Montenegro; Carlo Francesco Selmi, Maria De Santis, Angela Ceribelli, University of Milan, Italy; Ludmila Garzanova, Olga Koneva, Maya Starovoytova, VA Nasonova Institute of Rheumatology, Moscow, Russia; Ariane Herrick, University of Manchester, UK; Francesco Puppo, Simone Negrini, Giuseppe Murdaca, Università di Genova, Italy; Merete Engelhart, University Hospital of Gentofte, Hellerup, Denmark; Gabriela Szücs, Szilvia Szamosi, University of Debrecen, Hungary; Carlos de la Puente, Cristina Sobrino Grande, Maria Jesus Garcia Villanueva, Hospital Ramon Y Cajal, Madrid, Spain; Øyvind Midtvedt, Anna-Maria Hoffmann-Vold, Rikshospitalet University Hospital, Oslo, Norway; David Launay, Vincent Sobanski, Hôpital Claude Huriez, Lille, France; Valeria Riccieri, Massimiliano Vasile, Katia Stefantoni, 'Sapienza' Università di Roma, Italy; Ruxandra Maria Ionescu, Daniela Opris, Laura Groseanu St Maria Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Ami Sha, Adrianne Woods, Johns Hopkins School of Medicine, Baltimore, USA; Ana Maria Gheorghiu, Mihai Bojinca, Ion Cantacuzino Clinical Hospital, Bucharest, Romania; Cord Sunderkötter, Jan Ehrchen, University of Münster, Germany; Francesca Ingegnoli, Istituto Gaetano Pini, University of Milano, Italy; Luc Mouthon, Bertrand Dunogue, Benjamin Chaigne, Paul Legendre, Hôpital Cochin, Paris, France; Francesco Paolo Cantatore, Ada Corrado, U.O. Reumatologia-Università degli Studi di Foggia, Ospedale 'Col. D'Avanzo', Foggia, Italy; Susanne Ullman, Line Iversen, University Hospital of Copenhagen, Denmark; Carlos Alberto von Mühlen, Rheuma Clinic, Porto Alegre, Brazil; Maria Rosa Pozzi, Ospedale San Gerardo, Monza, Italy; Kilian Eyerich, Felix Lauffer, TU Munich, Germany; Piotr Wiland, Magdalena Szmyrka-Kaczmarek,

Renata Sokolik, Ewa Morgiel, Marta Madej, Wroclaw University of Medicine, Poland; Marie Vanthuyne, Houssiau Frédéric, Université Catholique de Louvain, Bussels, Belgium; Juan Jose Alegre-Sancho, Hospital Universitario Dr Peset, Valencia, Spain; Martin Aringer, Kristine Herrmann, Claudia Günther, Technical University of Dresden, Germany; Rene Westhovens, Ellen De Langhe, Jan Lenaerts, University Hospital Leuven, Belgium; Branimir Anic, Marko Baresic, Miroslav Mayer, University of Zagreb, Croatia; Maria Üprus, Kati Otsa, East-Tallin Central Hospital, Tallin, Estonia; Sule Yavuz, University of Marmara, Altunizade-Istanbul, Turkey; Brigitte Granel, Hôpital Nord de Marseille, France; Sebastião Cezar Radominski, Carolina de Souza Müller, Valderílio Feijó Azevedo, Hospital de Clinicas da Universidade Federal do Parana, Curitiba, Brazil; Fabian Mendoza, Joanna Busquets, Thomas Jefferson Scleroderma Centre, Philadelphia, USA; Sergei Popa, Svetlana Agachi, Republican Clinical Hospital, Chisinau, Republic of Moldova; Thierry Zenone, Unit of Internal Medicine, Valence, France; Margarita Pileckyte, Kaunas University of Medicine Hospital, Lithuania; Simon Stebbings, Sarah Jordan, Dunedin School of Medicine, New Zealand; Alessandro Mathieu, Alessandra Vacca, University of Cagliari-Policlinico Universitario, Cagliari, Italy; Percival D. Sampaio-Barros, University of São Paulo, Brazil; Lisa Stamp, University of Otago, Christchurch, New Zealand; Kamal Solanki, Cherumi Silva, Joanne Schollum, Helen Barns-Graham, Waikato University Hospital, Hamilton, New Zealand; Douglas Veale, Marie O'Rourke, St Vincent's University Hospital, Dublin, Ireland; Esthela Loyo, Carmen Tineo, Glenny Paulino, Hospital Regional Universitario Jose Ma Cabral y Baez, Santiago, Dominican Republic; Walid Ahmed Abdel Atty Mohamed, Alexandria University, Egypt; Edoardo Rosato, Antonietta Gigante, Università La Sapienza, Roma, Italy; Fahrettin Oksel, Figen Yargucu, Ege University, Izmir, Turkey; Cristina-Mihaela Tanaseanu, Monica Popescu, Alina Dumitrascu, Isabela Tiglea, Clinical Emergency Hospital St Pantelimon, Bucharest, Romania; Rosario Foti, Elisa Visalli, Alessia Benenati, Giorgio Amato, A.O.U. Policlinico Vittorio Emanuele La U.O. Di Reumatologia, A.O.U. Policlinico V.E. 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