Racial differences in SSc disease presentation: a European Scleroderma Trials and Research group study.

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Background

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

Methods

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

Results

9162 white, 341 Asian and 181 black patients were included.

Asian patients developed the first non-Raynaud's phenomenon (RP) feature faster than white, but slower than black patients. Asian patients were less likely to harbour anticentromere autoantibodies (ACA; OR=0.4, p<0.001) and slightly more likely to be anti-topoisomerase-I autoantibodies (ATA) positive (OR=1.2, p=0.068) while black patients were less likely to be ACA and ATA positive than white patients (OR[ACA]=0.3, p<0.001; OR[ATA]=0.5, p=0.020). Asian patients had less often (OR=0.7, p=0.06) and black patients (OR=2.7, p<0.001) more often diffuse skin involvement than whites.

Asian and black patients were more likely to have pulmonary hypertension (PH; OR[Asians]=2.6, p<0.001, OR[blacks]=2.7, p=0.03 vs whites) and a reduced forced vital capacity (FVC; OR[Asians]=2.5, p<0.001; OR[blacks]=2.4, p<0.004) than white patients. Asians more often had an impaired diffusing capacity for carbon monoxide than black or white patients (OR[Asians]=2.4, p<0.001; OR[blacks]=1.2, p=0.45). After RP onset, Asian and black patients had a higher hazard to die than white patients (HR[Asians]=1.6, p=0.011; HR[blacks]=2.1,p<0.001).

Conclusions

Compared to whites, Asians have a faster and earlier disease onset with high prevalences of ATA, PH and FVC impairment and a higher mortality. Black patients had the fastest disease onset, a high prevalence of diffuse skin involvement and nominally the highest mortality.
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 systemic sclerosis (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 to white SSc patients [4,5,7–9]. Data on black SSc patients however mostly stem from African Americans and figures 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; anticentromere antibodies (ACA) for example are frequent in Caucasian patients, whereas anti-topoisomerase-I antibodies (ATA) are highly prevalent in Choctaw Native Americans, Thais and African Americans [1,3,12,13]. Detailed cohort studies on SSc disease presentations in Asians are however 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 and the allocation of healthcare resources.

In this analysis of the multi-racial, multinational database of the European Scleroderma Trials and Research group (EUSTAR), we therefore aimed to investigate the effect of the patient’s race on SSc presentation and to simultaneously compare disease presentations of black patients living in and outside sub-Saharan Africa, as well as Asian patients living within and outside Asia.
METHODS

Study population

This study is based on the multinational, longitudinal EUSTAR database. The structure of the EUSTAR database has 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 if they fulfilled the 1980 ACR or 2013 ACR/EULAR criteria for SSc [21,22] and if information on the patient’s racial background (whites/Asians/blacks) were available. Patients who self-reported themselves as being of mixed race i.e. white/Asian or white/black, were adjudicated to the Asian or black patient group respectively. Information about the core data collected in EUSTAR can be found elsewhere [19,20].

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 white patients followed in the EUSTAR database vs all Asian patients vs all black patients in EUSTAR.

Second, we used a centre-matched approach in order to reduce possible effects of environmental factors and health care systems. In this approach, we compared Asian patients treated outside Asia with all white patients in the same centres and black patients treated outside sub-Saharan Africa with all white patients in the same centres.

In a third ‘individual-matched’ approach, we were matching 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 (±5yrs), sex, time since the onset of Raynaud’s phenomenon (RP, ±3yrs), time since the first non-RP manifestation (±3yrs) 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 and lastly, we compared Asian patients treated within Asia vs Asian patients treated outside Asia, and black patients treated within sub-Saharan Africa vs black patients 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 the onset of RP to the first non-RP manifestation of the disease, forced vital capacity (FVC; % of predicted) and FVC<80% of predicted as a proxy for a pulmonary restrictive defect, single-breath diffusing capacity for monoxide (DLCO/sb; % of predicted) and DLCO/sb<80% of predicted, systolic pulmonary arterial pressure as estimated by echocardiography (PAPsys; mmHg) and PAPsys>40mmHg as a proxy for suspected PH, modified Rodnan skin thickness score (mRSS), the extent of skin involvement, i.e. diffuse/limited, autoantibody status and finally mortality.

**Statistical analysis**

Frequencies/percentages or means/standard deviations (SD) were calculated; demographic and disease characteristics between racial groups were compared using $\chi^2$-tests/Fisher’s exact tests or ANOVA/Kruskal-Wallis tests. 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 was assessed by Kaplan-Meier methods and compared between the racial groups using log-rank tests. 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 one 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 manuscript are based on the imputed data, and all analyses were performed with Stata/IC 15.1 (StataCorp, College Station, Texas, USA).
RESULTS

Patient characteristics

Of the 14,601 patients followed in the EUSTAR registry by January 2018, 13,377 fulfilled the 1980 ACR or the 2013 ACR/EULAR criteria for SSc. Of those, 9,161 were white patients, 341 Asian patients, and 198 black patients and were hence included in this analysis. Of the Asian patients, 208 were recruited within Asia (EUSTAR centre Beijing, China) and 133 patients 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 (EUSTAR centre Johannesburg). Of the black patients, 82 were recruited within Africa and 116 patients within 35 centres outside Africa, 33 patients from 9 centres in the Americas and 83 patients from 26 centres in Europe.

In the centre-matched analyses, the 133 Asian patients from outside Asia were compared to 4,700 white patients being followed in the same centres than the Asian patients. Similarly, the 116 black patients followed outside Africa were compared to 3,824 white patients. In the individual-matched analyses, 337 Asian patients were matched to 337 white patients and 197 black patients were matched to 197 white SSc patients.

On average, Asian and black patients were ten years younger than white patients (p<0.001, Table 1). Of the white patients more were male (16%) than of the Asian or black patients (11%, 13%, respectively; Table 1).
Table 1. Demographic and disease characteristics by race.

ACA, anticentromere autoantibodies; ATA, anti-topoisomerase autoantibodies; DLCO/sb, single breath diffusing capacity for 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; RP, Raynaud’s phenomenon; SD, standard deviation

<table>
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<tr>
<th></th>
<th>Whites</th>
<th>Asians</th>
<th>Blacks</th>
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<td>N</td>
<td>9161</td>
<td>341</td>
<td>198</td>
<td></td>
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<tr>
<td>Age; mean years (SD)</td>
<td>56.7 (13.8)</td>
<td>46.3 (12.6)</td>
<td>45.6 (11.8)</td>
<td>&lt;0.001</td>
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<td>Age at RP onset; mean years (SD)</td>
<td>44.2 (15.4)</td>
<td>38.1 (13.3)</td>
<td>37.8 (12.2)</td>
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<td>Male sex; %</td>
<td>16.0</td>
<td>11.4</td>
<td>13.1</td>
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<td>Disease characteristics</td>
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<tr>
<td>Time since RP onset; median years (IQR)</td>
<td>9.2 (3.8-17.7)</td>
<td>5.2 (2.1-11.0)</td>
<td>5.9 (2.0-10.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>Time since first non-RP manifestation; median years (IQR)</td>
<td>6.5 (2.7-12.9)</td>
<td>4.1 (1.5-9.0)</td>
<td>5.4 (2.1-10.4)</td>
<td>&lt;0.001</td>
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<td>Time RP to non-RP; median years (IQR)</td>
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<td>0 (0-2.0)</td>
<td>0 (0-0.4)</td>
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<td>Sine</td>
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<td>Puffy fingers, ever</td>
<td>51.1</td>
<td>77.8</td>
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<td>Digital ulcers, ever</td>
<td>37.1</td>
<td>27.7</td>
<td>42.6</td>
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<td>Telangiectasia</td>
<td>59.2</td>
<td>44.3</td>
<td>18.0</td>
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<td>LVEF; median % (IQR)</td>
<td>61 (60-66)</td>
<td>68 (63-70)</td>
<td>60 (58-65)</td>
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<td>LVEF&lt;50</td>
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<td>PAPsys; mean mmHg (SD)</td>
<td>29 (15)</td>
<td>34 (17)</td>
<td>31 (16)</td>
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<td>PAPsys &gt;40mmHg; %</td>
<td>11.6</td>
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<td>DLCO/sb; mean % of predicted (SD)</td>
<td>69 (22)</td>
<td>61 (18)</td>
<td>66 (24)</td>
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<td>DLCO/sb &lt;80% of predicted; %</td>
<td>70.2</td>
<td>83.8</td>
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<td>FVC; mean % of predicted (SD)</td>
<td>95 (22)</td>
<td>82 (18)</td>
<td>81 (25)</td>
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<td>97.6</td>
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<td>46.5</td>
<td>34.1</td>
<td>&lt;0.001</td>
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<td>RNAP-III positive</td>
<td>4.7</td>
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<td>6.7</td>
<td>0.26</td>
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<td>Proteinuria</td>
<td>5.5</td>
<td>7.8</td>
<td>8.2</td>
<td>0.076</td>
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</table>
**Autoantibodies**

Comparing all Asian patients with all white patients, Asian patients were less likely to harbour ACA (OR=0.4, 95%CI 0.3-0.5, p<0.001) and slightly more likely 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 (Table 2; Table 3). Asian patients treated within Asia were comparably often ACA and ATA positive than Asian patients 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).

Black patients were less likely to be ACA and ATA positive than all white EUSTAR and individual-matched white patients (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, black patients were also less likely to harbour ACA, but similarly likely to be ATA positive than the centre-matched white patients (Table 2). Patients from the centre in Johannesburg were equally likely to be ACA positive than black patients 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, Asian patients harbour substantially less ACA and slightly more ATA than white patients, while black patients are less often ACA positive than white patients.

**Speed of disease onset**

Asian and black patients developed RP at a younger age than whites (Table 1). After the onset of RP phenomenon, black patients evolved with the first non-RP feature of SSc faster than Asian and white patients (Table 1, Figure 1a). Two years after the onset of RP, 66% of white patients (95%CI 65%-67%) had experienced their first non-RP SSc manifestation, compared to 74% of Asian patients (95%CI 69%-79%) and 87% of black patients (95%CI 82%-92%). These kinetics of a faster disease onset in black and Asian patients were also seen after adjustment for potentially confounding factors (HR[blacks] 1.4, 95%CI 1.2-1.5, p<0.001; HR[Asians] 1.1, 95%CI 1.0-1.2, p=0.009; both vs white patients; HR[blacks vs Asians] 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 black and white patients (HR [blacks] 1.3, 95%CI 1.1-1.5 p=0.001). Similarly, Asians evolved with their first non-RP manifestation slightly faster than
the centre-matched whites, even though this difference was only numerical (HR [Asians] 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 Asian patients treated outside Asia and those treated within Asia (Figure 1b). Similarly, there were no differences in the time to the first non-RP feature between black patients treated outside and those treated within sub-Saharan Africa (Figure 1c).

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

**Figure 1.** Kaplan-Meier curves with 95% CI of the first non-RP feature after RP onset according to (a) racial group; (b) geographical location of Asian patients (in Asia or outside Asia), (c) and geographical location of black patients (outside sub-Saharan Africa or within).

Patients who experienced their first non-RP feature of the disease before the onset of RP were attributed a simultaneous onset.
Skin involvement

The prevalence of diffuse skin involvement was similar between Asian and white patients, but higher in black patients (Table 1). In multivariable analysis, Asian patients had less often diffuse skin involvement than white patients (OR 0.7, 95%CI 0.5-1.0, p=0.06) while black patients were more likely to have diffuse disease than whites (OR 2.7, 95%CI 1.9-4.0, p<0.001). The same was seen when comparing diffuse skin status among Asian patients with that of individual-matched white patients (OR 0.5, 95%CI 0.4-0.8, p<0.001). However, when comparing the patients from outside Asia to the centre-matched white patients, the odds of diffuse skin involvement in Asian patients was comparable to that of these white patients (OR 1.1, 95%CI 0.7-1.7, p=0.57).
Black patients were more likely to have diffuse disease when compared to individual-matched white patients (OR 2.3, 95%CI 1.5-3.6, p<0.001). Similarly, black patients outside sub-Saharan Africa were more often of the diffuse subset than the centre-matched white patients (OR 2.4, 95%CI 1.5-3.8, p<0.001).

A similar pattern was apparent looking at the mRSS scores for Asian and black patients (Figure 2). Multivariately, white patients had a mRSS of 12, Asian patients of 10 and black patients of 14 (Figure 2a, p(white/Asians)<0.001; p(white/black)=0.015; p(Asians/blacks)<0.001).

To sum up, Asian patients tend to have less severe skin sclerosis than white patients, whereas black patients have a more severe skin involvement. The racial effect driving skin status appeared to be largely independent of geographical location.

**Figure 2.** Multiple adjusted levels of the outcome measures and corresponding 95% confidence intervals by racial status; panel (A) shows the results of all included patients, panel (B) of the centre-matched patients, panel (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 panel (D) comparing blacks from within sub-Saharan Africa and blacks from outside sub-Saharan Africa and Asian from within Asia and Asians from outside Asia.

Results illustrated in panel (A), (B) and (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 panel (C) are only adjusted for autoantibody status.

DLCO/sb, single breath diffusing capacity for 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.
Pulmonary interstitial and vascular involvement

The FVC (in % of predicted) was considerably lower in Asian and black patients than in white patients, both univariably and multivariably (Table 1; Figure 2). Asian patients and black patients were 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 to white patients. The same pattern of a lower FVC was seen comparing Asian patients with the centre-matched white patients (Figure 2b; Table 2) and when comparing Asian patients with the individual-matched white patients (Figure 2c; Table 3). The Asian patients treated in the EUSTAR centre in Beijing had a comparable FVC than the Asian patients treated outside Asia (Figure 2d).
The FVC was lower in black patients than in white patients (Figure 2a, b, c; Table 2; Table 3), but comparable to Asian patients. Interestingly, black patients treated outside sub-Saharan Africa had a considerably lower FVC than black patients followed in Johannesburg (Figure 2d).

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

The ORs represent Asian patients followed outside Asia (n=133) compared to all white patients of the EUSTAR centres in which the Asian patients were treated (n=4,700). The ORs of the black patients are based on the black patients followed outside sub-Saharan Africa (n=116) compared to all white patients of the EUSTAR centres in which the black patients were treated (n=3,824).

Results are adjusted for age, sex, time since the onset or 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).

ACA, anticientromere autoantibodies; ATA, anti-topoisomerase autoantibodies; CI, confidence interval; DLCO/sb, single breath diffusing capacity for 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; RP, Raynaud’s phenomenon.

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<th>Asians</th>
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<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
<td></td>
<td>OR</td>
<td>95%CI</td>
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<tr>
<td>Diffuse SSc</td>
<td>1.13</td>
<td>0.8-1.7</td>
<td>0.57</td>
<td>2.38</td>
<td>1.5-3.8</td>
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<td>FVC &lt;80% of predicted; %</td>
<td>3.85</td>
<td>2.6-5.7</td>
<td>&lt;0.001</td>
<td>4.16</td>
<td>2.8-6.3</td>
</tr>
<tr>
<td>DLCO/sb &lt;80% of predicted; %</td>
<td>3.10</td>
<td>1.7-5.5</td>
<td>&lt;0.001</td>
<td>1.97</td>
<td>1.2-3.3</td>
</tr>
<tr>
<td>PAPsys &gt;40mmHg; %</td>
<td>1.35</td>
<td>0.6-3.0</td>
<td>0.46</td>
<td>2.57</td>
<td>1.3-5.0</td>
</tr>
<tr>
<td>ACA positive</td>
<td>0.45</td>
<td>0.3-0.7</td>
<td>0.002</td>
<td>0.30</td>
<td>0.2-0.6</td>
</tr>
<tr>
<td>ATA positive</td>
<td>1.41</td>
<td>0.8-2.4</td>
<td>0.20</td>
<td>0.86</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>RNAP-III positive</td>
<td>1.29</td>
<td>0.5-3.4</td>
<td>0.60</td>
<td>0.91</td>
<td>0.3-2.6</td>
</tr>
</tbody>
</table>
Table 3. Multiple adjusted logistic regression results by racial status of the individual-matched patients.

The presented ORs of the Asian patients are based on 337 Asian patients and 197 black patients compared to 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).

ACA, anticentromere autoantibodies; ATA, anti-topoisomerase autoantibodies; CI, confidence interval; DLCO/sb, single breath diffusing capacity for 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; RP, Raynaud’s phenomenon.

<table>
<thead>
<tr>
<th></th>
<th>Asians</th>
<th></th>
<th></th>
<th>Blacks</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
<td>p-value</td>
<td>OR</td>
<td>95%CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Diffuse SSc</td>
<td>0.53</td>
<td>0.4-0.8</td>
<td>&lt;0.001</td>
<td>2.3</td>
<td>1.5-3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC &lt;80% of predicted; %</td>
<td>2.59</td>
<td>1.8-3.8</td>
<td>&lt;0.001</td>
<td>3.06</td>
<td>1.8-5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLCO/sb &lt;80% of predicted; %</td>
<td>2.53</td>
<td>1.7-3.8</td>
<td>&lt;0.001</td>
<td>1.12</td>
<td>0.7-1.9</td>
<td>0.68</td>
</tr>
<tr>
<td>PAPsys &gt;40mmHg; %</td>
<td>3.33</td>
<td>1.7-6.4</td>
<td>&lt;0.001</td>
<td>3.12</td>
<td>1.1-8.7</td>
<td>0.030</td>
</tr>
<tr>
<td>ACA positive</td>
<td>0.36</td>
<td>0.2-0.5</td>
<td>&lt;0.001</td>
<td>0.36</td>
<td>0.2-0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>ATA positive</td>
<td>1.36</td>
<td>1.0-1.9</td>
<td>0.057</td>
<td>0.67</td>
<td>0.4-1.0</td>
<td>0.063</td>
</tr>
<tr>
<td>RNAP-III positive</td>
<td>4.92</td>
<td>0.1-252.3</td>
<td>0.42</td>
<td>1.01</td>
<td>0.4-2.5</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Overall, Asian patients had considerably lower DLCO/sb levels than white patients, whereas the DLCO/sb levels in black patients were comparable to those of white patients (Table 1; Figure 2a). Asian patients were more likely to have a DLCO/sb of less than 80% of predicted than white patients (OR=2.4, 95%CI 1.8-3.3, p<0.001). This was also the case when comparing Asian patients treated outside Asia with white patients of the same centres (i.e. centre-matched; Figure 2b; Table 2) and when comparing Asian patients with their individual-matched white patients (Figure 2c; Table 3). In accordance with the above results, Asian patients treated within Asia had DLCO/sb levels similar to Asian patients treated outside Asia (Figure 2d; OR<80% of predicted]=0.6, 95%CI 0.3-1.3, p=0.17).

Black centre-matched (Figure 2b; Table2) patients had lower DLCO/sb levels than their white matched comparison group, however black individual-matched patients had comparable DLCO/sb levels than their white individual-matched comparison group (Figure 2c; Table 3). Black patients
treated within sub-Saharan Africa had significantly higher DLCO/sb levels than black patients being treated outside sub-Saharan Africa (Figure 2d; OR[<80% of predicted]=0.4, 95%CI 0.2-0.8, p=0.018).

With regards to PAPsys, Asian patients had higher levels than white patients (Table 1; Figure 2a). PAPsys levels were similar in black and white patients (Table 1; Figure 2a). Asian patients had 2.6 the odds of having a PAPsys greater than 40mmHg than white patients (95%CI 1.4-4.6; p=0.001). However, comparing Asian patients being treated outside Asia with the centre-matched white patients, this difference in PAPsys levels disappeared (Figure 2b, Table 2). Asian patients compared to their individual-matched white patients had higher PAPsys levels (Figure 2c, Table 3). Asian patients from within Asia had significantly higher PAPsys levels than Asian patients followed outside Asia (Figure 2d; OR[>40mmHg]=3.0, 95%CI 1.3-7.0, p=0.010).

Black patients treated outside sub-Saharan Africa had slightly higher PAPsys levels than white patients treated at the same centres (i.e. centre-matched; Figure 2b, Table 2). This difference was also apparent when comparing black patients with individual-matched white patients (Figure 2c, Table 3). Black patients from the centre Johannesburg had comparable PAPsys levels than black patients treated outside sub-Saharan Africa (Figure 2d; OR[>40mmHg]=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 onset of RP to either death or the last time the patient was known to be alive) of 12.5 years (IQR 6.5 to 21.4) in white patients, 9.8 years (IQR 6.1 to 15.5) in Asian patients and 8.6 years (IQR 3.9 to 14.4) in black patients. During this time, 12% of white patients, 9% of Asian patients and 13% of black patients died. Ten years after the first occurrence of RP, 6.5% of white patients (95%CI 6%-7%), 7.6% of Asian patients (95%CI 5%-12%) and 10.4% of black patients (95%CI 6%-17%) had died.

Asian patients as well as black patients had a higher hazard to die than white patients (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). Asian and black patients had a comparable hazard to die (HR 1.3, 95%CI 0.8-2.0, p=0.23). However, Asians had a comparable hazard to die in comparison to the white centre-matched patient group and in comparison to the white individual-matched patients (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). Asian patients from the centre in Beijing had a higher, but not
statistically significant higher, hazard to die (HR 1.5, 95%CI 0.7-3.4, p=0.34) than Asian patients outside Asia.

Black patients in the centre-matched approach had a slightly higher hazard to die than the white comparison group (HR 1.5, 95%CI 1.0-2.4, p=0.064). However, in the individual-matched approach, black patients had a comparable hazard to die than the matched white patient group (HR 1.4, 95%CI 0.7-2.7, p=0.34). Patients 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 black patients died faster and more frequently than white patients, irrespective of geographical location. Asian patients had also a slightly elevated mortality, which however partly disappeared in the matched analyses.
DISCUSSION

In this study of more than 9,000 white SSc patients, 341 Asian and 198 black SSc patients, several clinical and serological differences were evident between the three racial groups. We found that black patients had the fastest speed of disease onset but Asian patients developed the first non-RP feature faster than white patients. Compared with white patients, Asian patients had also a higher prevalence of PH and lung involvement.

The high prevalence of ATA in Asians independent of geographical location is in line with a Chinese study [16] and was also seen in Canada in patients of Chinese heritage in comparison with European descents (47% vs 27%, respectively; p = 0.02) [17]. In the Canadian study, the high prevalence of ATA was not reflected by an increased prevalence of ILD in Chinese descendants [17,26]. Contrasting this, we found that Asian race was consistently associated, univariably, but also after accounting for autoantibody profiles, with a depressed FVC, irrespective of treatment centre and geographical location. This finding was regardless of the analysis we applied and replicated by Asian studies which also found a high prevalence of ILD (80%) [16] and a fast evolution of lung involvement [27]. Although these differences might hint towards environmental factors or differences in the health care systems as an explanation for the ILD prevalences, our study, suggest a true genetic component.

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

In our study, Asians had higher prevalences of PH (PAPsys>40) than white patients. This finding was not seen when comparing Asians inside Asia vs. those outside, indicating that it is independent of geographical location. Our study also indicated a higher prevalence of PH in Asians than in individual-matched white patients. In a Chinese study including patients from the Chinese Rheumatism Data Centre, the prevalence of pulmonary arterial hypertension was similar to the PH prevalence 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% to 31%) compared to our study [28]. The authors, however, did not find a difference in PH prevalence between patients of various ethnicities [28]. This goes in line with our finding that Asian patients
treated outside Asia had a similar frequency of PH than 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 Asian patients had an increased mortality in multivariable analysis compared to white patients. This finding however partly disappeared in the matched analyses again being in line with the Canadian study which also found no difference in the survival time between ethnicities including white and Asian patients [28]. However, the compared patients were all residing in Canada. Hence, the result that Asian patients were likely to die faster in our study is likely to be partly attributable to environmental or socioeconomic factors or differences in health-care system.

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 completeness; only including patients with complete data into an analysis may lead to biased results depending on the reason of missingness [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 to rule out centre-specific differences in these continents. We can also not fully untangle the various factors associated with race including genetic and possibly behavioural factors. But we attempted to address possible environmental confounders and differences to health-care access by centre-matching and individual-matching and also by comparing the patients residing within their home continents to those living outside.

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


