Ethnic Variations in Systemic Sclerosis Disease Manifestations, Internal Organ Involvement, and Mortality

Haifa Al-Sheikh, Zareen Ahmad, and Sindhu R. Johnson

ABSTRACT. ***Objective.*** A multiethnic systemic sclerosis (SSc) cohort study to evaluate ethnic variations in disease manifestations, internal organ involvement, and survival.

Methods. Adults who fulfilled the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc between 1970 and 2017 were included. Self-reported ethnicity was categorized as European-descent white, Afro-Caribbean, Hispanic, Arab, East Asian, South Asian, First Nations, or Persian. The primary outcome was the time from diagnosis to death from all causes. Survival probabilities and median survival times were determined using Kaplan-Meier survival curves.

Results. There were 1005 subjects evaluated, the majority of whom were European-descent white (n = 745, 74%), Afro-Caribbean (n = 58, 6%), South Asian (n = 70, 7%), and East Asian (n = 80, 8%). Compared to European-descent white subjects, East Asians less frequently had calcinosis (29% vs 9%, p = 0.002) and esophageal dysmotility (88% vs 69%, p = 0.002); Afro-Caribbeans more frequently had interstitial lung disease (31% vs 53%, p = 0.007); and First Nations subjects more frequently had diffuse cutaneous disease (35% vs 56%, p = 0.02) and diabetes (5% vs 33%, p = 0.03). We found no difference in the short-term survival across ethnicities. Hispanic subjects have better longterm survival (81.3%, 95% CI 63–100) compared to European-descent white subjects (55%, 95% CI 51–60). East Asians appear to have the longest median survival time (43.3 yrs) and Arabs the shortest median survival time (15 yrs). There was no significant difference in median survival times between Afro-Caribbean and European-descent white subjects (22.2 vs 22.6 yrs).

Conclusion. Ethnic variations in some SSc disease manifestations are observed. However, this does not result in significant differences in short-term survival but may affect longterm survival. (J Rheumatol First Release March 1 2019; doi:10.3899/jrheum.180042)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS ETHNICITY

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Systemic sclerosis (SSc) is a systemic autoimmune rheumatic disease characterized by a pathological fibrosis of the skin, vasculopathy, and can involve multiple internal organs including the gastrointestinal tract, heart, lungs, and kidneys. The pathogenesis of SSc is a multifactorial process including alterations of the immune system, and genetic and environmental factors. The prevalence of SSc ranges from 7 to 489 per million and its incidence from 0.6 to 122 per million/year. Geographical variations in epidemiology have been described. SSc prevalence is higher in the United States (276/million in 1990) and Australia (233/million in 1999) than in Japan and Europe[1]. Studies have reported a higher incidence of SSc among African Americans compared to whites, with 22.5 cases/million/year and 12.8 cases/million/year, respectively[2].

The literature evaluating ethnic variation in disease manifestations, severity, and mortality in SSc is limited and

conflicted. Previous studies reported that African Americans have a younger age at disease onset, higher frequency of diffuse skin involvement, tendency for more severe disease manifestations, distinct serologic profile, and a worse prognosis compared to whites[3,4,5,6,7]. However, the latter finding is not consistent, as at least 1 report found the mortality after age adjustment did not differ significantly across the white and non-white groups, including African Americans[8].

Very few studies have examined the effect of SSc in other ethnic groups such as Hispanics, Arabs, and Asians. There are divergent results regarding disease manifestations among these racial groups compared to whites. Some studies suggested that the Hispanic and Thai patients with SSc are more likely to have diffuse skin disease and more severe disease compared with whites[9,10,11,12]. However, another study found no difference between Hispanics and whites[13]. The Japanese have a higher prevalence of severe pulmonary fibrosis compared to whites[14]. One study suggests that compared to whites, Chinese-descent patients have milder disease[15], whereas another study found that compared to US patients, Han Chinese patients with SSc more frequently have diffuse cutaneous disease and higher frequencies of Scl-70 and anti-U1RNP antibodies, but are lower in anticentromere and anti-RNA polymerase antibodies[16]. Data in the literature about other races with SSc such as Arabs and South Asians are sparse. One French study found that non-Europeans, which included a small number of Maghreb patients from Western North Africa, had disease manifestations different from those of Europeans[2].

The Toronto Scleroderma Program is a large, multiethnic cohort. Given the limited and conflicted previously published literature, the objectives of our study were to evaluate the effect of ethnicity on clinical manifestations and survival in SSc.

MATERIALS AND METHODS

Subjects. The Toronto Scleroderma Program is the largest single-center longitudinal SSc cohort in Canada. Patients were followed every 6 to 12 months using a standardized protocol[17]. Patients who fulfilled the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[18] and were 16 years of age or older were included in our cohort study. We excluded subjects with localized scleroderma (morphea), eosinophilic fasciitis, and undifferentiated connective tissue disease. The study period was between 1970 and 2017.

Exposure. Ethnicity was self-reported. Ethnicity was categorized as European-descent white, Afro-Caribbean, Hispanic, Arab, East Asian (including China, Japan, Korea, Philippines, and Thailand), South Asian (Bangladesh, Nepal, India, Pakistan, and Sri Lanka), First Nations, or Persian.

Outcomes. The primary outcome was the time from diagnosis to death from all causes. Dates of death were obtained from the clinic chart, hospital electronic record, or obituary. This approach as a source of mortality data had demonstrable validity and reliability[19], and has been used successfully in other research work[17,20,21,22,23].

Secondary outcomes included differences in disease duration (defined as the time from diagnosis of SSc to the death/censor date), subtype of SSc [limited SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) ascertained at baseline but revised if lcSSc evolved into dcSSc][24], calcinosis, Raynaud phenomenon (RP), digital ulceration, esophageal dysmotility (patient-reported symptoms of reflux, dysphagia, or food sticking retrosternally), telangiectasia, abnormal nailfold capillaries on visual inspection, interstitial lung disease [(ILD); forced vital capacity < 70%, and bibasilar reticular abnormalities with minimal ground glass on high-resolution computed tomography thorax][17], pulmonary arterial hypertension (PAH; mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg by right heart catheterization)[25], renal crisis (acute renal failure, new onset hypertension, normal or mild proteinuria on urinalysis, microangiopathic hemolytic anemia), and serology (topoisomerase I, centromere antibodies). All SSc subjects were screened with echocardiogram every 1–2 years. RNA polymerase III antibody was not evaluated because it is not available at our center.

Analysis. Descriptive statistics were used to summarize the clinical and serologic data. Pearson chi-square test with Yates' continuity correction was used to evaluate differences in proportions, and Kruskal-Wallis rank-sum test was used to evaluate differences in means. Subjects who were alive as of January 1, 2017, were censored. Survival rates for 1 to 5 years, and 10, 15, and 20 years, and median survival rates were determined using Kaplan-Meier survival curves. Cox proportional hazards models were used to estimate survival adjusting for era of treatment, age and disease duration, and comorbidities (hypertension, coronary artery disease, and diabetes). Multiple comparisons were accounted for using a Bonferroni corrected p value of ≤ 0.002.

Data quality. Data were collected from the clinic chart and/or electronic medical record onto a standardized data collection form and double-entered into a computerized database. Internal logic and range checks were used to ensure data accuracy.

Ethics. This study complies with the Declaration of Helsinki. Research ethics board (REB) approval was obtained prior to the conduct of this study (REB no. 16-0298-C). Consent was waived owing to the high mortality in this cohort study.

RESULTS

Subjects. There were 1005 subjects evaluated, the majority of whom were European-descent white (n = 745, 74%), Afro-Caribbean (n = 58, 6%), South Asian (n = 70, 7%), East Asian (n = 80, 8%), Hispanic (n = 30, 3%), Arab (n = 9, 0.9%), First Nations (n = 7, 0.7%), and Persian (n = 6, 0.6%). The majority of subjects were female (n = 823, 82%). Three hundred sixty-six subjects (36%) had dcSSc. The mean disease duration in this cohort was 11.7 years. European-descent white, Afro-Caribbean, East Asian, and Hispanic subjects had comparable disease duration, whereas South Asians has statistically significantly shorter disease duration ($p < 0.001$; Table 1).

Clinical manifestations. A comparison of demographics, disease manifestations, and comorbidities is summarized in Table 1. In comparison to European-descent white subjects, East Asians had less frequent calcinosis (29% vs 9%, $p = 0.002$) and esophageal dysmotility (88% vs 69%, $p = 0.002$); Afro-Caribbeans more frequently had ILD (31% vs 53%, $p = 0.007$) and less telangiectasia (81% vs 45%, $p < 0.001$); First Nations subjects more frequently had diffuse cutaneous disease (35% vs 56%, $p = 0.02$) and diabetes (5% vs 33%, $p = 0.03$). There were no differences across ethnicities in the prevalence of RP, pulmonary hypertension, renal crisis, or digital ulcers. Anticentromere antibody was present

Table 1. Comparison of disease manifestations and internal organ involvement across ethnicities.

Variables	European-descent White, n = 745	Afro-Caribbean, n = 58	South Asian, n = 70	East Asian, n = 80	Hispanic, n = 30	Arab, n = 9	First Nations, n = 7	Persian, n = 6	p
Demographics									
Diffuse subtype	261 (35)	28 (48)	21 (30)	39 (49)	9 (30)	3 (33)	5 (56)	0 (0)	0.02
Female sex	609 (82)	47 (81)	56 (81)	64 (80)	26 (87)	8 (89)	7 (78)	6 (100)	0.78
Disease duration, mean, yrs	12.8	10.2	7.5	10.0	11.2	10.2	9.2	12.2	< 0.001*
Age at diagnosis, mean, yrs	47.1	41.0	45.8	48.2	47.9	42.3	35.6	43.0	0.01
Clinical manifestations									
Calcinosis	219 (29)	12 (21)	15 (21)	7 (9)	6 (20)	3 (33)	3 (33)	1 (17)	0.002*
Raynaud phenomenon	715 (96)	54 (93)	66 (94)	73 (91)	29 (97)	9 (100)	7 (100)	6 (100)	0.55
Esophageal dysmotility	652 (88)	54 (93)	59(84)	55 (69)	27 (90)	8 (89)	7 (100)	5 (83)	0.002*
Sclerodactyly	710 (95)	53 (91)	63 (90)	68 (85)	27 (90)	9 (100)	7 (100)	6 (100)	0.01
Telangiectasia	601 (81)	26 (45)	46 (66)	45 (57)	23 (77)	6 (67)	5 (56)	4 (67)	< 0.001*
Interstitial lung disease	234 (31)	31 (53)	32 (46)	33 (41)	11 (37)	3 (33)	4 (44)	1 (17)	0.007
Pulmonary hypertension	198 (27)	16 (28)	19 (27)	25 (31)	6 (20)	2 (22)	3 (33)	0 (0)	0.82
Scleroderma renal crisis	44 (6)	4 (7)	6 (9)	1 (1)	1 (3)	0 (0)	0 (0)	1 (17)	0.36
Abnormal nailfold capillary	236 (32)	23 (40)	37 (53)	25 (31)	11 (37)	1 (11)	2 (22)	1 (17)	0.02
Digital ulcers	263 (35)	19 (33)	21 (30)	21 (26)	12 (40)	2 (22)	2 (22)	2 (33)	0.71
Antibodies									
Scl-70 antibody	111 (15)	19 (33)	17 (24)	28 (35)	3 (10)	4 (44)	2 (22)	4 (67)	< 0.001*
Anticentromere antibody	155 (21)	1 (2)	13 (17)	18 (23)	13 (43)	1 (11)	1 (11)	2 (33)	0.001*
Comorbidities									
Coronary artery disease	70 (9)	0 (0)	4 (6)	3 (4)	2 (7)	0 (0)	1 (11)	0 (0)	0.09
Systemic hypertension	154 (21)	9 (16)	13 (19)	14 (18)	4 (13)	0 (0)	3 (33)	1 (17)	0.65
Diabetes mellitus	39 (5.2)	3 (5.2)	7 (10)	4 (5)	0 (0)	0 (0)	3 (33)	1 (17)	0.03
Hyperlipidemia	45 (6)	1 (2)	8 (11)	3 (4)	2 (7)	2 (22)	0 (0)	0 (0)	0.16
Peripheral vascular disease	34 (5)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	1 (17)	0.05
Cancer	90 (12)	3 (5)	2(3)	7 (9)	3 (10)	1 (11)	0 (0)	0 (0)	0.19
Stroke	21 (3)	1 (2)	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0.86
Atrial fibrillation	25 (3)	3 (5)	1 (1)	2 (3)	1 (3)	0 (0)	0 (0)	0 (0)	0.90

Values are expressed as n (%) unless otherwise indicated. Clinical manifestations and comorbidities occurred at any time. Disease duration was determined from date of diagnosis. Pearson chi-square test was used to evaluate differences in proportions, and Kruskal-Wallis rank-sum test was used to evaluate differences in means. * Denotes statistical significance after Bonferroni correction for multiple comparisons.

in 204 (20.3%) of total patients and was least common in Afro-Caribbeans (21% vs 2%, p = 0.001). In comparison, Scl-70 was present in n = 188 subjects (18.7%), and least common in Hispanics (10%, p < 0.001).

Survival. In our cohort, there were 471 deaths. Survival probabilities and median survival time are summarized in Table 2. We found no difference in the unadjusted short-term survival across ethnicities (Figure 1).

Hispanic subjects have better longterm survival (81.3%, 95% CI 63–100) compared to European-descent white subjects (55%, 95% CI 51–60). East Asians appear to have the longest median survival time (43.3 yrs) and Arabs the shortest median survival time (15 yrs). There was no significant difference in median survival times between Afro-Caribbean and European-descent white subjects (22.2 vs 22.6 yrs).

Exploratory Cox regression analyses adjusting for era of treatment, age, and disease duration, and comorbidities (coronary artery disease, hypertension, and diabetes) resulted in no significant change in the hazard ratios across ethnicities (Table 3).

DISCUSSION

Ethnic variations in SSc disease characteristics, internal organ involvement, and survival have implications for monitoring, treatment, and prognosis[26]. We found that in comparison to European-descent white subjects, East Asians less frequently had calcinosis cutis, esophageal dysmotility, sclerodactyly, and telangiectasia. Afro-Caribbean subjects more frequently had ILD and less telangiectasia than European-descent whites. East Asian, Afro-Caribbean, and First Nations subjects appear to more frequently have diffuse cutaneous disease compared to European-descent white subjects. There were no differences across ethnicities in the prevalence of RP, pulmonary hypertension, renal crisis, or digital ulcers.

Interestingly, despite differences in SSc manifestations, we found no difference in short-term survival across ethnicities. Hispanic subjects have better longterm survival compared to European-descent whites. East Asians appear to have the longest median survival time and Arabs the shortest median survival time. We found no significant difference in median survival times between Afro-Caribbean and European-descent white subjects.

Table 2. Comparison of systemic sclerosis survival probabilities and median survival time across ethnicities.

Probability of Survival	European-descent White	Afro-Caribbean	South Asian	East Asian	Hispanic	Arab	First Nations	Persian
1-yr	98 (97–99)	97 (92–100)	95 (90–100)	99 (96–100)	96 (89–100)	100 (100)	100 (100)	100 (100)
2-yr	96 (95–97)	89 (82–98)	92 (85– 99)	97 (94–100)	96 (89–100)	100 (100)	100 (100)	100 (100)
3-yr	94 (93–96)	89 (82–98)	90 (83–98)	97 (94–100)	96 (89–100)	100 (100)	87 (67–100)	100 (100)
4-yr	91 (89–94)	88 (79–97)	88 (80–97)	94 (89–100)	96 (89–100)	100 (100)	87 (67–100)	100 (100)
5-yr	89 (86–91)	88 (79– 97)	88 (80–97)	94 (89–100)	96 (89–100)	100 (100)	87 (67–100)	100 (100)
10-yr	78 (74–81)	72 (60–87)	78 (67–91)	75 (64–88)	89 (76–100)	71 (45–100)	87 (67–100)	100 (100)
15-yr	69 (65–73)	67 (53–85)	74 (61–89)	72 (60–86)	81 (63–100)	71 (45–100)	58 (25–100)	100 (100)
20-yr	55 (51–60)	61 (46–82)	53 (32–87)	68 (55–84)	81 (63–100)	0.0 (0)	58 (25–100)	100 (100)
Median survival time, yrs (IQR)	22 (20–25)	22 (18–NA)	NA (19–NA)	43 (NA)	NA (NA)	15 (8–NA)	NA (11–NA)	NA (NA)

Values are expressed as % (95% CI) unless otherwise indicated. Survival rates and median survival rates were determined using Kaplan-Meier analyses. NA: not available; IQR: interquartile range.

Results of 2 studies have suggested that Afro-Caribbeans with SSc have worse survival compared to European-descent whites[3,27]. A study by Laing, *et al* demonstrated an increase in mortality in African Americans, which was significant even after adjustment for age and disease subtype[5]. In comparison, Steen, *et al* demonstrated a variation in survival between African Americans and European-descent whites, which they attributed to autoantibody profile and the presence

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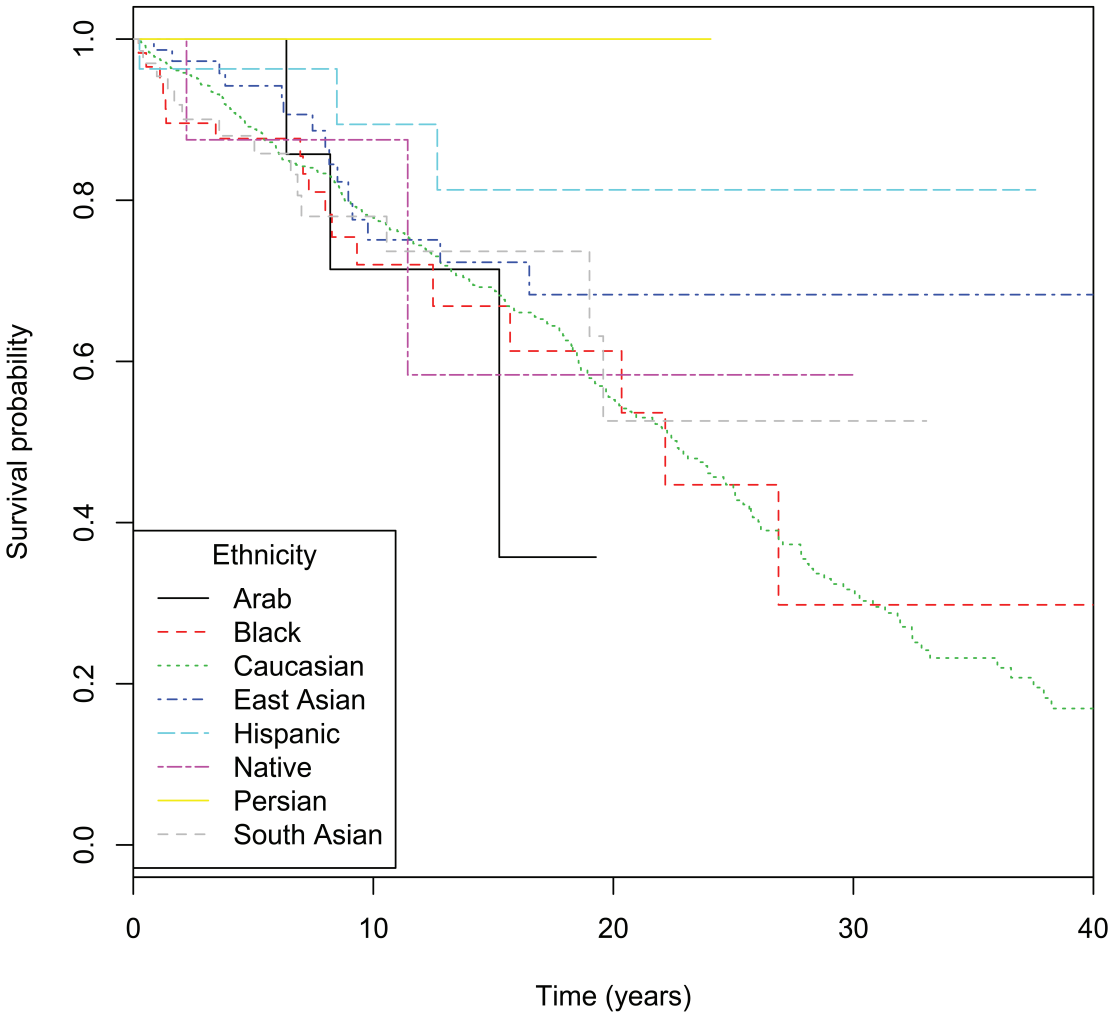

Figure 1. Comparison of Kaplan-Meier survival curves across ethnicities.

Table 3. Unadjusted and adjusted systemic sclerosis survival by ethnicity.

Survival	European-descent White	Afro-Caribbean	South Asian	East Asian	Hispanic	First Nations
Unadjusted	1.27 (0.25–2.46)	1.21 (0.24–2.82)	1.28 (0.22–2.72)	1.78 (0.16–1.93)	0.43 (0.05–1.16)	0.16 (0.11–3.84)
Adjustment for era	1.13 (0.28–2.76)	1.32 (0.22–2.58)	1.42 (0.20–2.46)	1.90 (0.15–1.81)	0.45 (0.04–1.10)	0.16 (0.11–3.83)
Adjustment for age at diagnosis and disease duration	1.22 (0.26–2.57)	0.85 (0.34–3.99)	1.02 (0.28–3.43)	1.90 (0.15–1.81)	0.39 (0.05–1.28)	0.54 (0.30–11.13)
Adjustment for coronary artery disease, hypertension, and diabetes	1.40 (0.23–2.34)	1.26 (0.23–2.71)	1.33 (0.21–2.61)	1.94 (0.15–1.78)	0.48 (0.04–1.03)	0.19 (0.09–3.22)

Values are HR (95% CI).

of ILD[7]. In the Johns Hopkins Scleroderma Center cohort, the cumulative incidence of mortality during 10 years of followup was significantly higher in African Americans compared to European-descent whites[28]. However, the mortality risk estimates diminished between the 2 ethnicities when accounting for sex, disease subtype, scleroderma-specific autoantibody status, socioeconomic status, and health insurance status. In our cohort, we found no difference in the short-term survival across ethnicities. Our study occurred in the setting of a publicly funded, universal healthcare system where all citizens and permanent residents are eligible for public health insurance. This suggests that ethnic variation in disease manifestations does not affect short-term survival. Previously observed differences may be partially attributable to access to care. This is consistent with our previous finding of no ethnic differences in survival in systemic lupus erythematosus (SLE) at our center, whereas ethnic differences in SLE survival were reported at other centers without universal healthcare[26]. In the long term, our data did suggest possible differences in survival. This may be attributable to cultural variations in health-seeking behaviors, adherence, and cultural medical practices.

Disease duration has been hypothesized to be a confounder because some SSc clinical manifestations occur later in the disease such as calcinosis cutis, PAH, and telangiectasia. In our study, disease duration did not appear to confound the relationship for clinical manifestations and ethnicity. East Asians had decreased frequency of calcinosis cutis but comparable disease duration to whites, and South Asians had increased frequency of calcinosis cutis and shorter disease duration. Further, despite differing disease durations across ethnicities, there was no difference in the frequency of PAH.

Our study has a number of strengths. First, the Toronto Scleroderma cohort is a multiethnic cohort reflecting the immigration patterns of Toronto, Canada. This presents a unique opportunity to compare ethnicities that are not represented in other large SSc cohorts. Indeed, this has been a recognized limitation of the EUSTAR cohort (European League Against Rheumatism Scleroderma Trials and Research group), among others. Second, our cohort has longterm followup (> 40 yrs) with well-characterized survival data — again a unique opportunity compared to other SSc cohorts. Our study may be affected by potential limitations. Because of the small number of individuals of Arab, First Nations, and Persian ethnicity, the statistical significance seems to be driven primarily by the major ethnic groups (European-descent white, Afro-Caribbean, South Asian, and East Asian). Although we report interesting findings within the smaller ethnic groups, definitive statements are precluded. Second, we were unable to account for the psychosocial determinants of health, because that was outside the scope of our study. It is possible that apparent differences in clinical manifestations could be explained by social factors. For example, fewer First Nations patients with limited disease seek out medical care, and their prevalence could be underestimated. The effect of psychosocial determinants of health in SSc is an area that warrants further consideration.

Ethnic variations in SSc disease manifestations and internal organ involvement are observed. However, in the setting of a universal healthcare system, this does not result in significant differences in survival. Other factors may affect perceived differences in longterm survival in selected ethnic groups. Our findings may inform patient counseling, appropriate baseline screening, aggressiveness of monitoring, and future study design[29]. Understanding ethnic variations in disease outcomes will improve our ability to provide personalized medicine.

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