

# Ethnic Influence on Disease Manifestations and Autoantibodies in Chinese-Descent Patients with Systemic Sclerosis

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**ABSTRACT. Objective.** To investigate ethnic influence on disease manifestations and autoantibody profile in patients of Chinese descent with systemic sclerosis (SSc).

**Methods.** In a retrospective study of a multiethnic SSc cohort followed over a 17-year period, disease manifestations and autoantibody profile of patients of European and Chinese descent were compared.

**Results.** There were 300 patients of European descent and 36 of Chinese descent, with similar proportions of women (81% and 72%, respectively) and patients with diffuse SSc (50% and 56%). Patients of Chinese descent [mean age  $\pm$  standard deviation (SD) 52  $\pm$  16 yrs;  $p = 0.05$ ] were diagnosed at an older age compared to patients of European descent (mean  $\pm$  SD 46  $\pm$  12 yrs). Patients of Chinese descent compared to those of European descent had less frequent joint (69% vs 86%;  $p = 0.01$ ) and gastrointestinal involvement (78% vs 94%;  $p = 0.004$ ), but increased prevalence of myositis (17% vs 5%;  $p = 0.01$ ). Patients of Chinese descent had less frequent digital ulceration (36% vs 55%;  $p = 0.04$ ), and an absence of renal crisis. The frequency of cardiac and pulmonary involvement was similar in both groups. More patients of Chinese than of European descent were positive for anti-topoisomerase-I (47% vs 27%;  $p = 0.02$ ), anti-Ro (36% vs 10%;  $p = 0.001$ ), and anti-U1RNP (17% vs 5%;  $p = 0.03$ ) antibodies. The observed differences for anti-topoisomerase-I, anti-Ro, and joint and gastrointestinal manifestations persisted in the subgroup analysis of patients matched for sex, disease subtype, and age at diagnosis.

**Conclusion.** Patients of Chinese descent have milder SSc disease with less frequent joint and gastrointestinal manifestations, less severe vasculopathy, but increased prevalence of myositis and certain autoantibodies. Research is needed to identify determinants (genetic, environmental, and cultural factors) of the relationship between ethnicity and disease. (J Rheumatol First Release Feb 15 2009; doi:10.3899/jrheum.080915)

## Key Indexing Terms:

SYSTEMIC SCLEROSIS      CHINESE      ETHNIC GROUPS      AUTOANTIBODIES

Systemic sclerosis (SSc) is an autoimmune disease of unknown cause characterized by skin thickening, microvascular injury, and fibrosis, leading to multiple organ damage. Ethnicity has a significant influence on the epidemiology, clinical manifestations, survival, autoantibody frequencies, and genetic factors in SSc<sup>1</sup>. By understanding the variation of these factors with ethnicity, appropriate treatment, monitoring, and prognostication may be possible.

The highest prevalence of SSc is in Choctaw Native Americans (660 per million)<sup>2</sup>, followed by those of African

descent (315 per million)<sup>3</sup> and European descent (31 to 286 per million), with the lowest estimates in Japanese patients (21 to 53 per million)<sup>4</sup>. Data from multiethnic cohorts (including African Americans, Hispanics, and Choctaw Native Americans) suggest that subjects of non-European descent are more likely to have severe disease, especially diffuse SSc (dSSc) and pulmonary involvement<sup>5-7</sup>. African Americans develop disease earlier and are more likely to have dSSc, digital ulcers, digital pitting, pulmonary arterial hypertension (PAH), impaired lung function, pericarditis, and higher mortality<sup>1,3,5-8</sup>.

Ethnic differences in autoantibody frequencies have also been reported. Anticentromere antibodies (ACA) are more frequent in Caucasian subjects<sup>1</sup>, whereas anti-topoisomerase-I antibodies have the highest frequencies in Choctaw Native Americans (71%)<sup>2</sup>, Thais (41%–76%)<sup>9,10</sup>, and African Americans (38%)<sup>8,11</sup>. The latter are also more likely to have anti-Ro and anti-U1RNP antibodies<sup>8</sup>. In a well defined subset of patients with dSSc identified by the presence of anti-topoisomerase-I, Kuwana, *et al*<sup>12</sup> found that ethnicity had an independent effect on the severity of lung

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disease and survival, with patients of Japanese and African origin having poorer prognosis.

Studies conducted in Asia have included patients of Indian<sup>13</sup>, Thai<sup>9,10,14,15</sup>, Japanese<sup>12,16,17</sup>, and Korean origin<sup>18</sup>, with none available in the English literature on Chinese subjects. Toronto is a multiethnic city of nearly 4.7 million people (2001 census), with those of Chinese and African descent making up 10% and 7% of the population, respectively<sup>19</sup>. Ninety percent of Chinese Canadians trace their origins to Hong Kong (45.6%), mainland China (27.7%), Taiwan (11.8%), and Vietnam (5.2%)<sup>19</sup>. The Canadian healthcare system presents a unique opportunity to study the influence of ethnicity on SSc because data would be less influenced by differential healthcare access, as universal healthcare coverage is available to all citizens and landed immigrants, with no cost to patients for primary care or specialist consultations.

With the advantages of a large Chinese-descent population in Toronto and a unique healthcare system, we specifically investigated whether there were ethnic differences in disease manifestations between SSc patients of Chinese descent and those of European descent. This is the first study of Chinese patients with SSc, and would contribute to the existing literature, which strongly suggests that ethnicity has a significant effect on the disease.

## MATERIALS AND METHODS

**Patient selection.** Patients registered in the University of Toronto SSc clinic between January 1, 1990, and September 30, 2007, as part of a longitudinal cohort, were included in our study if they (1) fulfilled American College of Rheumatology (ACR) classification criteria for SSc<sup>20</sup> or were diagnosed with SSc as part of an overlap syndrome with systemic lupus erythematosus (SLE) fulfilling ACR criteria for SLE; (2) were of European or Chinese descent; and (3) were seen in the clinic on more than 1 occasion. Patients were excluded if (1) age at diagnosis was  $\leq 18$  years or (2) they were of African descent or other East Asian (Filipino, Japanese, and Korean), South or West Asian origin. An inflammatory arthritis with a pattern resembling that of rheumatoid arthritis and myositis were considered to represent another disease manifestation of SSc, and not an overlap syndrome with SSc. Ethnicity was self-reported. This remains a valid method of ethnic categorization in research<sup>21</sup>.

**Data collection.** Medical records of eligible patients were reviewed for: (1) demographic data, including sex, ethnicity, disease subtype according to the LeRoy 1988 classification<sup>22</sup>, age at diagnosis, disease duration at last followup or death, and followup period; (2) initial visit and subsequent peak modified Rodnan skin score (mRSS)<sup>23</sup>; (3) clinical manifestations of SSc as defined below; (4) treatment history [ever use of peripheral vascular, gastrointestinal (GI), or PAH therapies, corticosteroids, and immunosuppression]; and (5) investigations, including autoantibody profile, pulmonary function tests, computed tomography (CT) of the lung and echocardiogram. Disease onset was defined from the time of physician's diagnosis of SSc fulfilling ACR criteria. Self-reported ethnicity was recorded as European descent or Chinese descent.

**Clinical manifestations of SSc.** Clinical manifestations of SSc were documented as follows: (1) joint involvement was defined as any one of joint tenderness, joint swelling, joint contracture, tendon friction rub, or tenosynovitis; (2) peripheral vascular involvement was defined as any one of Raynaud's phenomenon, digital pitting, digital ulcers, or digital gangrene; (3) myositis was defined as the presence of proximal muscle weakness on

examination and either a raised serum creatine kinase, characteristic electromyogram (with abnormal myopathic low amplitude, short-duration polyphasic motor potentials, increased insertional activity, and spontaneous fibrillations or complex repetitive discharges), or muscle biopsy; (4) cardiac involvement was defined as any one of pericarditis (pericardial pain plus either the presence of a pericardial rub or pericardial effusion), cardiomyopathy, congestive heart failure or arrhythmia requiring treatment; (5) GI involvement was defined as the presence of symptoms or investigations confirming gastroesophageal reflux, GI dysmotility, bacterial overgrowth, or malabsorption; (6) interstitial lung disease (ILD), diagnosed on CT thorax, lung biopsy, or pulmonary function test<sup>24</sup> defined as a forced vital capacity (FVC)  $< 80\%$  predicted plus forced expiratory volume in 1 s (FEV1)/FVC  $> 80\%$ , and diffusing capacity for carbon monoxide (DLCO)  $< 75\%$  predicted in the presence of unexplained exertional dyspnea; (7) PAH defined by a right ventricular systolic pressure (RVSP)  $\geq 40$  mm Hg on echocardiogram; and (8) scleroderma renal crisis (SRC) defined as acute renal failure associated with the abrupt onset of moderate to severe hypertension in the absence of other causes of renal failure. Disease durations at the time of ILD, PAH, and SRC diagnoses were calculated. As a reflection of disease severity for ILD and PAH, the trough FVC and peak RVSP for each patient were recorded.

**Autoantibody profile.** The presence of antinuclear antibody (ANA), ACA, anti-topoisomerase-I, anti-Smith, anti-Ro, anti-La, anti-U1 ribonucleoprotein (anti-U1RNP), anti-Jo1, anti-double-stranded DNA (dsDNA), and rheumatoid factor (RF) was recorded from the medical chart.

**Statistical analysis.** Comparisons between ethnic groups were made using chi-squared or Fisher's exact tests for categorical variables, and the 2-sample t test or nonparametric Mann-Whitney U test for continuous variables. Subgroup analysis of ethnic groups matched for sex, disease subtype (diffuse or limited SSc, diffuse or limited SSc-SLE overlap syndromes), and age at diagnosis within 10 years was performed to investigate significant findings on initial analysis. *p* values less than 0.05 were considered statistically significant. All analyses were performed using SPSS version 11.5.

Our study was approved by the institutional research ethics board and is in compliance with the Helsinki Declaration.

## RESULTS

**Patient demographics.** Of 572 patients registered within the study period, there were 300 patients of European (78%) and 36 (8%) of Chinese descent. This closely reflects their population prevalence in Toronto. The majority of patients of Chinese descent in the cohort originated from Hong Kong, mainland China, or Vietnam. Eighty-one patients not fulfilling ACR criteria, 70 patients of other ethnic origin, 75 who were seen in clinic only once, and 10 who were diagnosed  $\leq 18$  years of age were excluded.

The patients of European and Chinese descent had similar proportions of women (81% and 72%) and patients with diffuse SSc (50% and 56%). The median initial and peak mRSS were similar in patients of Chinese [13 (range 0–40) and 19 (range 2–40), respectively] and European descent [12 (range 0–45) and 17 (range 2–45)]. Patients of Chinese descent were diagnosed at an older age [mean  $\pm$  standard deviation (SD)  $52 \pm 16$  yrs; *p* = 0.05] compared to patients of European descent ( $46 \pm 12$  yrs). At entry to the cohort, the median disease duration from the time of SSc diagnosis was 0.1 years in patients of Chinese descent compared to 0.7 years in those of European descent (*p* < 0.001), and the duration of Raynaud's phenomenon was 2.4 and 3.3 years,

respectively ( $p = 0.14$ ). At entry, the percentage of patients with probable SSc who subsequently fulfilled ACR criteria was 5.6% ( $n = 2$ ) among the patients of Chinese descent (after a range of 0.2 to 7.1 yrs) and 2.3% ( $n = 7$ ) among the patients of European descent (after a range of 0.1 to 1.1 yrs). Patients of Chinese descent had significantly shorter median disease duration at last visit/death of 4 years (range 0.1–17.3 yrs;  $p < 0.001$ ) compared to 9 years (range 0.2–46.5 yrs) in patients of European descent. Median duration of followup in patients of Chinese descent was 3 years (range 0.1–19.1 yrs) versus 5 years (range 0–35.8 yrs) in patients of European descent ( $p = 0.03$ ).

**Autoantibody profile.** Comparing patients of Chinese and European descent, the former had more patients with positive anti-topoisomerase-I (47% vs 27%;  $p = 0.02$ ), anti-Ro (36% vs 10%;  $p = 0.001$ ), and anti-U1RNP (17% vs 5%;  $p = 0.03$ ) antibodies (Figure 1). Concomitant anti-topoisomerase-I and ACA were seen in 3 Chinese women with dSSc. One patient was considered to have SSc-SLE overlap based on leukopenia, thrombocytopenia, malar rash, and positive anti-Smith and anti-U1RNP. All 3 had initial mRSS of 26 (peak 27 to 33), peripheral vascular involvement [Raynaud’s phenomenon ( $n = 3$ ), digital ulcers ( $n = 2$ ), digital pitting ( $n = 3$ )], arthritis, and GI involvement. One patient with ILD and PAH died of PAH after 9 years of disease.

**Disease manifestations.** The frequency of peripheral vascular involvement overall, cardiac, and PAH involvement was similar between both groups, with an absence of SRC in patients of Chinese descent (Table 1). SSc-SLE overlap syndrome occurred in 3 (1%) patients of European descent and

5 (14%) of Chinese descent. Fewer patients of Chinese than European descent had digital ulcers (36% vs 55%;  $p = 0.03$ ), joint manifestations (69% vs 86%;  $p = 0.01$ ), and GI involvement (78% vs 94%;  $p = 0.004$ ). However, more patients of Chinese than European descent had myositis (17% vs 5%;  $p = 0.01$ ). Among patients with myositis and available serology for anti-U1RNP, 40% (2 of 5) of patients of Chinese descent and 17% (2 of 12) of patients of European descent had positive anti-U1RNP. ILD was diagnosed earlier in patients of Chinese descent [median 0.3 yrs (range –4.9–9.0 yrs)] compared to patients of European descent [median 1.8 yrs (range –10.0–28.6 yrs);  $p = 0.056$ ], with similar median trough FVC in both groups (65% and 71% predicted). Patients of European descent with PAH had higher median peak RVSP of 57 mm Hg (range 40–120 mm Hg) compared to patients of Chinese descent, with median peak RVSP of 46 mm Hg (range 40–69 mm Hg;  $p = 0.01$ ; Table 1). Comparing patients of Chinese and European descent, there was no difference in median time to diagnosis of PAH from the first onset of Raynaud’s phenomenon [median 8.7 yrs (range 1.6–19.8 yrs) and median 7.4 yrs (range –0.08 to 60.2 yrs), respectively;  $p = 0.86$ ].

**Subgroup analysis of patients matched for sex, disease subtype, and age at diagnosis.** A total of 70 patients of European descent were matched to 35 of Chinese descent. One man of Chinese descent with SSc was excluded from this analysis, as no patient match of European descent was found for the late age at diagnosis of 82 years. The increased prevalence of anti-topoisomerase-I (48% vs 13%;  $p < 0.001$ ) and anti-Ro antibodies (37% vs 6%;  $p = 0.001$ ) remained significant in patients of Chinese compared to European

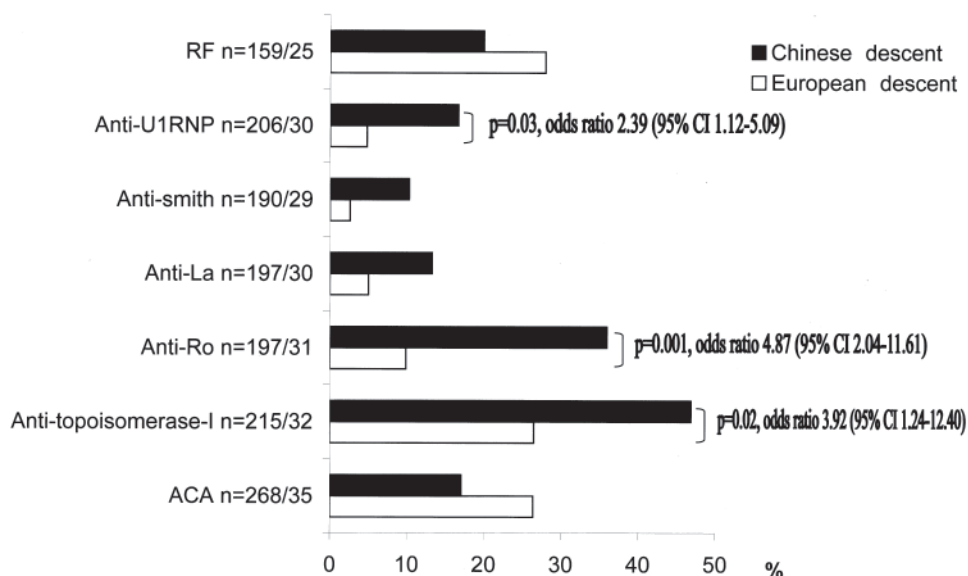


Figure 1. Comparing patients of Chinese and European descent, the former had more patients with positive anti-topoisomerase-I (47% vs 27%;  $p = 0.02$ ), anti-Ro (36% vs 10%;  $p = 0.001$ ), and anti-U1RNP (17% vs 5%;  $p = 0.03$ ) antibodies.

Table 1. Ethnic differences in disease manifestations.

Disease Manifestations	European-descent n = 300	Chinese-descent n = 36	p Value*	Odds Ratio (95% CI)
Joint	257 (85.7)	25 (69.4)	0.01	0.38 (0.17–0.83)
Digital pits	218 (72.7)	23 (63.9)	0.27	0.67 (0.32–1.38)
Digital ulcers	166 (55.3)	13 (36.1)	0.03	0.46 (0.22–0.94)
Digital gangrene	31 (10.3)	3 (8.3)	1.00	0.79 (0.23–2.72)
Raynaud's phenomenon	298 (99.3)	36 (100)	NA	
Myositis	14 (4.7) <sup>†</sup>	6 (16.7)	0.01	4.07 (1.46–11.38)
Gastrointestinal	281 (93.7)	28 (77.8)	0.004	0.24 (0.10–0.59)
Cardiac	34 (11.3)	4 (11.1)	1.00	0.98 (0.33–2.94)
ILD	97 (32.6) <sup>†</sup>	11 (30.6)	0.81	0.91 (0.41–1.93)
Median trough FVC % predicted (range)	71 (22–143)	65 (45–76)	0.22**	
PAH	70 (25.1) <sup>†</sup>	11 (30.6)	0.48	1.31 (0.62–2.81)
Median peak RVSP mm Hg (range)	57 (40–120)	46 (40–69)	0.01**	
Renal crisis	20 (6.7) <sup>†</sup>	0	NA	

ILD: interstitial lung disease, PAH: pulmonary arterial hypertension, NA: not applicable, CI: confidence interval. Group comparisons made using chi-squared or Fisher's Exact test (p\*) and Mann-Whitney U-test (p\*\*). Frequencies = n (%), unless otherwise stated. <sup>†</sup> Total numbers analyzed in European-/Chinese-descent patients for myositis = 299/36, ILD = 298/36, PAH = 279/36, and renal crisis = 298/36.

descent, but not for anti-U1RNP (17% vs 6%; p = 0.14). Decreased frequency of joint manifestations (69% vs 86%; p = 0.04) and GI involvement (77% vs 96%; p = 0.006) was observed in patients of Chinese compared to European descent. The observed differences in digital ulcers and myositis did not reach statistical significance (Table 2).

**Treatment.** Fewer patients of European descent (46%) were ever treated with corticosteroids compared to patients of Chinese descent (64%; p = 0.05). Fewer patients of Chinese than European descent were ever treated for their peripheral vascular (44% vs 71%; p = 0.001) or GI (61% vs 79%; p = 0.01) manifestations. Ever-use of immunosuppressive treatment (most frequently methotrexate, azathioprine, and cyclophosphamide) was not significantly different between patients of Chinese (58%) and European descent (52%).

## DISCUSSION

Understanding the determinants of disease in patients with SSc of different ethnicities has implications for appropriate treatment, monitoring, and prognostication. Patients of Chinese descent in our study were diagnosed later and had increased frequency of anti-topoisomerase-I compared to patients of European descent, factors that would predict poorer survival<sup>3,25</sup>, and more severe ILD<sup>26</sup>. However, except for the increased prevalence of myositis, patients of Chinese descent had less frequent joint and GI involvement and digital ulceration. Joint involvement in our study included any one of joint tenderness, joint swelling, joint contracture, tendon friction rub, or tenosynovitis. We did not differentiate joint contractures from the other joint manifestations because joint tenderness/swelling/tenosynovitis in SSc may be difficult to determine accurately by examination due to

Table 2. Ethnic differences in autoantibody profile and disease manifestations matched for sex, disease subtype and age at diagnosis.

Outcome	European-descent n = 70	Chinese-descent n = 35	p Value	Odds Ratio (95% CI)
Autoantibodies				
Anti-topoisomerase-I*	7 (13.0)	15 (48.4)	< 0.001	6.30 (2.18–18.20)
Anti-Ro*	3 (6.1)	11 (36.7)	0.001	8.88 (2.22–35.43)
Anti-U1RNP*	3 (6.1)	5 (17.2)	0.14	3.19 (0.70–14.52)
Disease manifestations				
Joint	60 (85.7)	24 (68.6)	0.04	0.36 (0.14–0.97)
Digital ulcers	38 (54.3)	13 (37.1)	0.10	0.50 (0.22–1.14)
Myositis	5 (7.1)	6 (17.1)	0.17	2.69 (0.76–9.53)
Gastrointestinal	67 (95.7)	27 (77.1)	0.006	0.15 (0.04–0.61)

CI: confidence interval. Group comparisons made using chi-squared or Fisher's Exact test. Frequencies = n (%), unless otherwise stated. \* Total numbers analyzed in European-/Chinese-descent patients for anti-topoisomerase-I = 54/31, anti-Ro = 49/30, and anti-U1RNP = 49/29.

overlying skin tightness or contractures. This is supported by an observational pilot study we conducted comparing clinical findings to magnetic resonance imaging of the hand in SSc (unpublished data). Among patients with myositis, the majority were negative for anti-U1RNP, and therefore unlikely to have mixed connective tissue disease. Whether myositis occurring in patients with SSc represents another disease manifestation or indicates an overlap syndrome is unknown, but does not greatly affect the clinical management of these patients. True inflammatory myositis may have been overestimated in our cohort as not all patients with proximal muscle weakness and raised creatine kinase (which would have fulfilled our definition of myositis in this study) had confirmatory electromyogram or muscle biopsy.

Patients of Chinese descent had similar frequency of PAH as those of European descent, but appeared to have less severe PAH based on lower median peak RVSP. Although the shorter duration of followup in patients of Chinese descent may result in an underestimation of the frequency of PAH, the disease duration at the time of PAH diagnosis was not statistically significant between the 2 groups. PAH in our cohort was defined based on echocardiogram, and confirmation with right-heart catheterization was not always carried out, although necessary prior to treatment. Overall, patients of Chinese descent appear to have fewer complications with SSc-associated vasculopathy. Decreased frequency of Raynaud's phenomenon in one study of Thai patients<sup>9</sup> was attributed to warmer climate, but would not explain the decreased peripheral vascular involvement in patients of Chinese descent in our study, where subjects were similarly exposed to the cold climate in Canada. Subgroup analysis of the 2 ethnic groups matched for sex, disease subtype, and age at diagnosis showed that the differences remained significant for joint and GI manifestations. It is uncertain whether the absence of scleroderma renal crisis in patients of Chinese descent is clinically significant, due to the small sample size and low incidence of this complication. There was a trend towards patients of Chinese descent developing earlier onset ILD.

It is interesting, therefore, to find significantly more patients of Chinese descent with positive anti-Ro, anti-U1RNP, and anti-topoisomerase-I compared to their counterparts of European descent. The prevalence of anti-Ro in SSc is 10% to 37%<sup>27</sup>, with increased expression reported for African Americans, suggesting ethnic influence on antibody prevalence<sup>8</sup>. Anti-Ro antibodies in patients with SSc have been associated with increased frequency of sicca or Sjögren's syndrome<sup>16,27,28</sup>, and polymyositis<sup>28</sup>. As sicca syndrome was not systematically recorded or investigated in our cohort, it is difficult to determine from our study whether the high prevalence of anti-Ro in patients of Chinese descent is associated with Sjögren's syndrome. Anti-Ro antibodies may occur on the basis of an SSc-SLE overlap syndrome. Of 11 patients of Chinese descent with

positive anti-Ro, 3 had SSc-SLE overlap syndrome and 1 was positive for anti-U1RNP without clinical features of an overlap syndrome. Of 20 patients of European descent with positive anti-Ro antibodies, 1 had SSc-SLE overlap.

In a study of lip biopsy-proven Sjögren's syndrome in SSc<sup>27</sup>, only patients with characteristic lymphocytic infiltrates had positive anti-Ro and/or anti-La, whereas patients with glandular fibrosis were negative for the antibodies, and had significantly higher mortality related to more severe, although not necessarily more frequent visceral complications of SSc. Hence the presence of anti-Ro suggests better prognosis in patients with SSc. This was confirmed in a study of anti-topoisomerase-I-positive patients with SSc, where anti-Ro was negatively associated with poor survival and progression to severe lung disease<sup>12</sup>. It is interesting to speculate that the high prevalence of anti-Ro in patients of Chinese descent with SSc may confer a better prognosis in this population. In contrast, patients of African descent with SSc have more severe disease and a poorer prognosis, but have increased prevalence of anti-Ro antibodies. The significance of anti-Ro antibodies in different ethnic groups needs to be explored.

Anti-U1RNP occurs in 2% to 14%<sup>29</sup> of patients with SSc and is often found in association with an overlap syndrome or mixed connective tissue disease. The increased frequency of anti-U1RNP (17%) may explain the higher prevalence of SSc-SLE overlap syndrome (14%) in patients of Chinese descent. The observed difference in frequency, however, was no longer significant in the matched ethnic group comparison, possibly due to matching of disease subtype.

Three patients of Chinese descent with dSSc had coexisting ACA and anti-topoisomerase-I, a rare phenomenon occurring in < 0.5% of patients with SSc<sup>30</sup>. The occurrence of these 2 antibodies is considered to be mutually exclusive, with each defining a clinical subtype, and having different HLA associations<sup>30</sup>. Patients who co-express these antibodies often have dSSc and immunogenetic features of both antibody-defining SSc subtypes. Whether this heralds poorer prognosis in this subgroup of patients is unclear.

The frequency of anti-topoisomerase-I was significantly higher in patients of Chinese than of European descent, a finding that persisted in the matched ethnic group comparison. The increased frequency of anti-topoisomerase-I, a known risk factor for ILD, was not reflected by an increase in prevalence of ILD in patients of Chinese descent, although they had an earlier onset of ILD. One proposed mechanism of anti-topoisomerase-I in the pathogenesis of SSc is that these antibodies recognize topoisomerase-I (released from apoptotic endothelial cells) bound to fibroblast cell surface<sup>31</sup>, resulting in downstream activation of monocytes with increased release of profibrotic cytokines. Ethnic variation in the avidity and epitope targets of topoisomerase-I as seen in comparative studies involving Thai<sup>14</sup> and Japanese<sup>12</sup> patients may explain the differential clinical

effect of anti-topoisomerase-I seen in different ethnic groups.

Autoantibody associations with SSc subgroups and manifestations vary according to diagnostic techniques<sup>31</sup>. Due to different diagnostic laboratory determinations of antibody profile (depending on the referral source), and missing data for several antibodies, inferences regarding prevalence and association of these antibodies with disease manifestations between the ethnic groups should be interpreted with caution, and require confirmation in a prospective study using uniform techniques for all patients. In our institution, ANA were detected using indirect immunofluorescence; anti-Ro, anti-La, anti-Smith, and anti-U1RNP were detected using immunodiffusion; and anti-topoisomerase-I was detected using ELISA. There were significant differences in the percentage of missing data between the 2 ethnic groups in the initial analysis for anti-topoisomerase-I, anti-Ro, anti-La, and anti-Smith antibodies, but not for the subsequent matched analysis. As the study population is drawn from a tertiary referral institution, referral bias may result in patients with more severe disease in our cohort than those seen in the community. Another caution in interpreting the results in the context of multiple comparisons made in this study is that the positive findings may have occurred by chance. A more conservative adjusted p value for statistical significance may have been applied. We argue that many of our findings may indeed be correlated, and in this setting, use of a p value correction may be excessively conservative<sup>32</sup>. To our knowledge, our study is the first to report differences in disease manifestations and autoantibody profile in patients with Chinese descent relative to those of European descent. Although the retrospective design of the study and the small number of patients of Chinese descent limit definitive conclusions, these provocative findings are hypothesis-generating, and serve as the necessary foundation for an adequately powered prospective study to further investigate this area.

Patients of Chinese descent in our cohort had milder disease based on less frequent joint and GI manifestations, less severe vasculopathy, specifically digital ulcers, PAH, and the absence of SRC involvement. Milder disease has also been reported in Thai patients<sup>10</sup> despite high prevalences of dSSc and anti-topoisomerase-I<sup>9</sup>. Despite the patients of Chinese descent having milder disease, there was an increase in use of corticosteroids in this cohort. While the reasons for this are uncertain, the higher frequency of myositis requiring treatment may have been a factor. It remains to be investigated whether patients of Chinese descent have better overall survival.

Ethnicity, likely linked to genetic and environmental factors and cultural perceptions, appears to influence the clinical manifestations and serological status in SSc. Our study contributes to the existing body of evidence pointing towards the significant effect of ethnicity on the pathogene-

sis of SSc. Research is needed to identify determinants of the relationship between ethnicity and disease.

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