The Effect of Male Sex on Survival in Systemic Sclerosis

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ABSTRACT. ***Objective.*** Systemic sclerosis (SSc) has a female predominance, however, little is understood about the effect of sex on SSc manifestations and survival. The objectives of our study were to evaluate differences in disease manifestations, and survival rates between males and females with SSc.

Methods. A retrospective cohort study of the Toronto Scleroderma Program was conducted to evaluate sex-based differences in disease manifestations and survival. A relative survival analysis compared SSc survival to the general population.

Results. There were 959 patients (791 females, 168 males) identified, with a female:male ratio of 4.7:1. Males more frequently had diffuse SSc [45% vs 30%, relative risk (RR) 1.44, 95% CI 1.18–1.75] and interstitial lung disease (ILD; 41% vs 33%, RR 1.24, 95% CI 1.01–1.52). There were 324 deaths (65 males, 259 females). Males had increased unadjusted mortality compared to females (HR 1.57, 95% CI 1.19–2.06). In an adjusted model including immunosuppressive use, male sex (HR 1.40, 95% CI 1.06–1.85), ILD (HR 1.58, 95% CI 1.26–1.98), and older age at diagnosis (HR 1.05, 95% CI 1.04–1.06) were independently associated with increased mortality, whereas the limited subtype (HR 0.70, 95% CI 0.49–0.77) and anticentromere antibodies (HR 0.70, 95% CI 0.49–0.98) were independently associated with decreased mortality. Male sex was associated with increased risk of mortality (HR 1.16, p = 0.003) in patients with SSc above that observed for males in the general population.

Conclusion. The differential effect of disease between sexes is small, yet males have decreased survival compared to females with SSc. (First Release Oct 1 2014; J Rheumatol 2014;41:2193–200; doi:10.3899/jrheum.140006)

Key Indexing Terms:

SCLERODERMA | SYSTEMIC SCLEROSIS | MORTALITY
SURVIVAL | MALE SEX | RENAL CRISIS

Systemic sclerosis (SSc) is a multisystem disease characterized by immune activation, fibrosis, and vascular abnormalities that can affect the skin and internal organs[1]. It can lead to loss of function, disability, and decreased quality of life[2]. The pathogenesis of SSc involves multifactorial processes, including immune system alterations, and genetic and exogenous factors[1]. It has a higher frequency in females than males, with a prevalence of 3:1–4:1 and a peak incidence between the ages of 45 and 64 years[1,3,4,5]. Little is known about how these sex differences affect clinical outcome in SSc, including onset, progression, and prognosis.

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The effect of sex on disease manifestations and patient outcomes is starting to be recognized among rheumatic diseases. Sex-based differences in disease and patient outcomes are a consequence of genetic differences that are attributable to the sex chromosomes and to differences in sex hormones[6,7]. Sex-based disparities in the immune response affect both the innate and adaptive immune responses[7]. Sex differences have been seen in arthritis. Females are at disproportionately higher risk than males for arthritis-related disability[8]. Similarly, it has been recognized that there are clinical differences between female and male patients with systemic autoimmune rheumatic diseases, such as systemic lupus erythematosus[9].

In the setting of SSc, sex has been proposed as a prognostic factor. However, the literature evaluating this is limited to small observational studies. Clinical studies have shown predictors of reduced survival including male sex[1,3,10,11,12,13,14,15,16,17,18,19,20], elevated erythrocyte sedimentation rate[15], older age at SSc onset[21], diffusing capacity of the lung[16,22], cardiac disease[15,23], renal disease[15,23], and malignancy[11,24,25,26,27,28,29,30]. It has also been suggested that the risk of mortality is greatest in the first few years of the disease[3,15,23,31]. While anticentromere antibody is associated with less severe organ involvement[1,4,5,10,21], anti-U3 RNP is associated with an increased risk of diffuse cutaneous disease (dcSSc),

pulmonary arterial hypertension (PAH), and muscle involvement, and is seen more commonly in males[17,32,33]. Very little is known about the effect of psychosocial factors (healthcare-seeking behavior and effect on disease) across sexes in SSc.

The aim of our study was to determine whether sex differences in SSc exist. The primary objective was to evaluate the effect of male sex on survival in SSc. The secondary objectives of our study were to determine whether males have an earlier age of onset, and evaluate differences in disease manifestations and serology between males and females.

MATERIALS AND METHODS

Patients. The Toronto Scleroderma Program, a health network comprising 3 academic hospitals (Toronto Western Hospital, Mount Sinai Hospital, Toronto General Hospital, Toronto, Ontario, Canada), is the largest single-center longitudinal cohort in Canada. Patients were followed every 6 to 12 months using a standardized protocol. Patients who fulfilled the American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[34] and were 16 years of age or older were included in our retrospective cohort study. We excluded patients with localized scleroderma (morphea), overlap syndromes, and undifferentiated connective tissue disease. The study period was 1970–2013.

Exposure. Sex was defined as a self-reported biological and physiological characteristic at birth, and categorized as male or female[28,35]. Gender (roles, behaviors, activities, and attributes that a given society considers appropriate, i.e., man vs woman) was not assessed[35]. Patients were excluded from the analysis if they had a known history of sex chromosome abnormalities (e.g., Klinefelter syndrome, Turner syndrome) or had undergone sex reassignment surgery.

Outcomes. The primary outcome was the time from diagnosis to death from all causes. Patients who were alive as of May 1, 2013, were censored. Dates of death were obtained from the clinic chart, hospital electronic record, or obituary. Online obituary Websites were searched to identify patients who had died. The date of death from the obituary was used if there was a correct match on the first name, last name, sex, city/town, and use of the term "scleroderma" in the obituary text. If a patient was alive for the last scheduled clinic visit, the family/referring physicians were contacted using a standardized letter that was faxed and mailed twice, and up to 2 subsequent telephone calls. Information about survival status, cause of death, or date last seen was collected. This approach to tracking patients who have been lost to followup and as a source of mortality data has been successfully used in other research work[30,36].

Secondary outcomes included sex differences in disease duration (defined as the time from diagnosis of SSc to the death/censor date), subtype of SSc [limited (lcSSc) or dcSSc, ascertained at baseline, but revised if lcSSc evolved into dcSSc)[37], calcinosis, Raynaud phenomenon, digital ulceration, symptomatic esophageal dysmotility on history, 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][36], PAH (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg by right heart catheterization)[38], renal crisis [acute renal failure, new onset hypertension (HTN), normal or mild proteinuria on urinalysis, microangiopathic hemolytic anemia], serology (topoisomerase, centromere antibodies), and immunosuppressive treatment. RNA polymerase III antibody was not evaluated because it is not available at our center.

Analysis. Descriptive statistics and RR with 95% CI were used to summarize the clinical and serologic data. Pearson's chi-squared test with Yates' continuity correction was used to evaluate differences in proportions, and Welch 2-sample t test was used to evaluate differences in means. Patients who were alive on May 1, 2013, were right-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 confounders that were found to be important in the published literature and have baseline differences in our cohort data on univariate analysis. We conducted a relative survival analysis to compare the survival experience of our cohort compared to the general Canadian population[39]. Using the Human Mortality Database, life tables for males and females from Statistics Canada (1921–2009) were obtained[40]. Additive models were used to account for age, sex, and year of diagnosis[39]. Analysis was conducted using RStudio (version 0.97.248)[41]. Research ethics board approval was obtained prior to the conduct of our study.

Data quality. All data were collected using a standardized data collection form and double-entered into a computerized database. Internal logic and range checks were used to ensure data accuracy.

RESULTS

Patients. The study included 1130 patients, who were screened to identify 959 patients with SSc [n = 791 females (82%) and n = 168 males (18%)]. Two of the excluded patients had a history of sex chromosome abnormalities and 1 had undergone sex reassignment surgery. The female to male ratio was 4.7:1. The female:male sex ratio by disease subtype was 3.1:1 for dcSSc and 6:1 for lcSSc. Males had significantly shorter mean (SD) disease duration than females (9.6 ± 8.8 yrs for males vs 12.4 ± 9.6 yrs for females, $p < 0.001$). There was no significant difference in age at diagnosis (males 48.3 ± 17.7 yrs vs females 50.0 ± 22.1 yrs, $p = 0.29$).

Disease manifestations and treatment. Males more frequently had diffuse cutaneous SSc (45% vs 30%, RR 1.44, 95% CI 1.18–1.75) and ILD (41% vs 33%, RR 1.24, 95% CI 1.01–1.52), and were treated with methotrexate (17% vs 11%, RR 1.51, 95% CI 1.03–2.22), but less frequently had anticentromere antibodies (ACA; 8% vs 18%, RR 0.46, 95% CI 0.28–0.78; Table 1).

Survival. There were 324 deaths (n = 65 males, n = 259 females). The mean ± SD age of death for males was 57.8 ± 11.9 years and for females, 60.5 ± 13.9 years. There was no statistically significant difference in the absolute proportion of deaths between sexes [females 259/791 (32.7%) vs males 65/168 (38.7%), $p = 0.88$]. The median survival time was 16.7 years for males and 24.2 years for females (Table 2). There was a significant difference in Kaplan-Meier survival curves between males and females (log rank test $p < 0.001$; Figure 1).

Unadjusted Cox regression found males had increased mortality compared to females (HR 1.57, 95% CI 1.19–2.06). In an adjusted model including immunosuppressive use, male sex (HR 1.40, 95% CI 1.06–1.85), presence of ILD (HR 1.58, 95% CI 1.26–1.98), and older age at diagnosis (HR 1.05, 95% CI 1.04–1.06) were independently associated with an increased risk of mortality,

Table 1. Summary of SSc cohort characteristics.

Disease Characteristics	Male, n = 168, n (%)	Female, n = 791, n (%)	RR (95% CI)
Baseline characteristics			
Diffuse subtype	76 (45)	236 (30)	1.44 (1.18–1.75)*
Disease manifestations			
PAH	56 (33)	312 (39)	0.85 (0.67–1.06)
Renal crisis	15 (9)	53 (6)	1.41 (0.81–2.45)
Abnormal nailfold capillaries	49 (29)	194 (25)	1.19 (0.91–1.55)
Digital ulcers	57 (35)	252 (32)	1.06 (0.84–1.34)
Scl-70 antibody	30 (18)	105 (13)	1.35 (0.93–1.95)
Anticentromere antibody	14 (8)	142 (18)	0.46 (0.28–0.78)*
Calcinosis	48 (29)	222 (28)	1.08 (0.78–1.33)
Raynaud phenomenon	157 (93)	757 (96)	0.98 (0.94–1.02)
Esophageal dysmotility	149 (89)	671 (85)	1.04 (0.98–1.11)
Telangiectasia	132 (79)	591 (75)	1.05 (0.96–1.14)
Interstitial lung disease	69 (41)	263 (33)	1.24 (1.01–1.52)*
Treatment			
Calcium channel blocker	148 (88)	700 (88)	0.99 (0.94–1.06)
Cyclophosphamide	12 (7)	41 (5)	1.37 (0.74–2.57)
Azathioprine	10 (6)	44 (6)	1.10 (0.46–2.65)
Methotrexate	29 (17)	90 (11)	1.51 (1.03–2.22)*

*95% CI that does not cross 1. SSc: systemic sclerosis; RR: relative risk; Scl-70: topoisomerase; PAH: pulmonary arterial hypertension.

Table 2. SSc survival by sex. Values are % (95% CI) unless otherwise specified.

Survival	Males, n = 168	Females, n = 791
Short term		
1 yr	96.9 (94.1–99.6)	98.7 (97.9–99.5)
2 yrs	92.4 (88.3–96.6)	96.4 (95.1–97.8)
3 yrs	90.4 (85.5–95.1)	94.8 (93.2–96.4)
4 yrs	87.5 (82.4–92.9)	93.0 (91.2–94.9)
5 yrs	84.6 (79.0–90.6)	90.6 (88.5–92.8)
Longterm		
10 yrs	68.7 (60.9–77.4)	79.4 (76.3–82.7)
15 yrs	56.2 (47.1–67.2)	70.8 (67.0–74.7)
20 yrs	42.8 (32.7–56.2)	58.1 (53.5–63.1)
Median, yrs	16.7	24.2

SSc: systemic sclerosis.

whereas the limited subtype (HR 0.70, 95% CI 0.49–0.77) and ACA (HR 0.70, 95% CI 0.49–0.98) were independently associated with a decreased risk of mortality.

Exploratory analyses were conducted to evaluate the effect of postmenopausal status. Among patients diagnosed with SSc after 45 years of age, males had an increased risk of mortality (adjusted HR = 1.9, p = 0.006). Cause of death, when available, is outlined by sex in Table 3. There was no difference between males and females in loss to followup [35/168 (21%) vs 207/791 (26%), p = 0.18], and all patients had a censor date for the survival analysis. Given the 40-year span of our cohort, we conducted a sensitivity analysis to evaluate for the presence of calendar or period effects. In the adjusted Cox model, the addition of a period variable to take into account decade of diagnosis did not result in a change in effect of male sex on survival (period adjusted sex HR 1.43, 95% CI 1.07–1.90). A relative survival analysis comparing the survival of the SSc cohort to the Canadian general population, accounting for sex, age, and year of diagnosis, found that males with SSc have an increased risk of death (HR 1.16, p = 0.003) compared to males in the general population.

DISCUSSION

We have found differences in disease prevalence, disease expression, and prognosis between males and females with SSc. In our cohort, the female to male ratio was 4.7:1. This is similar to, but slightly higher than, the previous estimates of 3:1 to 4:1[42]. The female:male sex ratio estimates vary when evaluating subsets of patients with SSc. Patients with limited disease have estimates ranging from 5:1 to 12:1[43,44], and in patients with dcSSc, disease estimates range from 4:1 to 5.7:1. In women in their childbearing years, the ratio has been reported to be 15:1[42], but lowers to 2.4:1 after menopause[45].

We found a differential burden in disease manifestations between sexes. We found that males more frequently had diffuse cutaneous SSc and ILD, but less frequently had ACA. One potential difference between male and female patients with SSc that was not evaluated in our study was exposure to solvents, other chemicals, and vibrating tools used in the workplace. Future investigators may evaluate their effect on age of disease onset, clinical and serological features, and/or survival.

Mortality for SSc has been estimated to be 4 times greater than that of the general population[14,18], and there

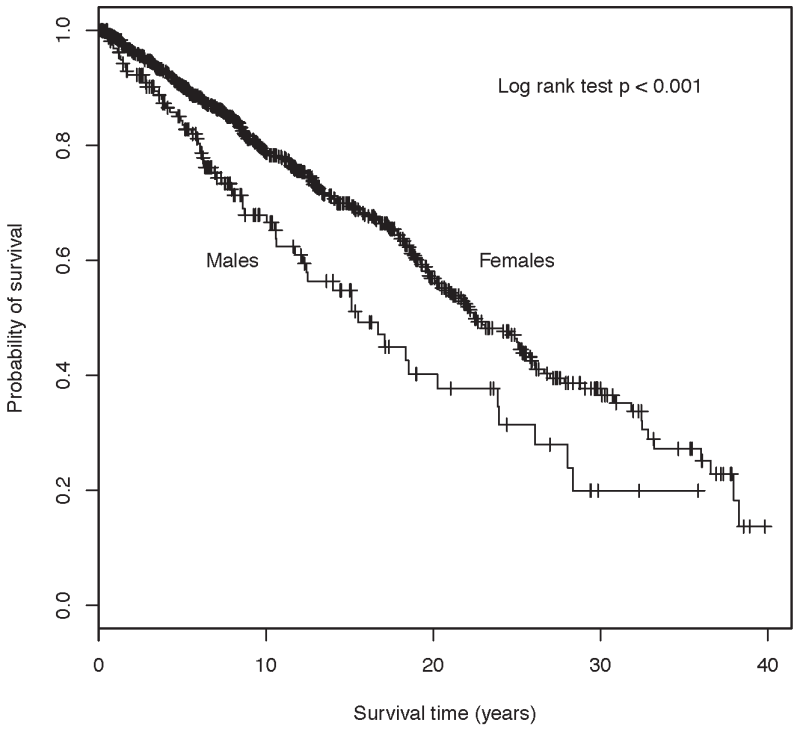

Figure 1. Kaplan-Meier survival curves for males and females with systemic sclerosis.

have been studies evaluating whether male sex portends a worse prognosis for patients with SSc. Many of the studies were too small in their patient numbers to make inferences and report conflicting results. Some observational studies indicated that males had worse survival rates than females[1,3,15,16,18,20,46,47,48,49,50], with higher association with malignancy, pulmonary complications, and a shorter survival once SSc had been diagnosed. Other study results report no statistical differences in survival between males and females[51,52,53]. The few studies that report the survival rates and disease manifestations between sexes are summarized in Table 4 and Table 5. Our study comprised a large cohort of patients, which gave our study the power to look at the effect of male sex on all-cause mortality, and we found that males have an increased mortality compared to females. At 5 years, survival rates were relatively close. With longer followup, the survival curves diverge at the 10-year, 15-year, and 20-year endpoints. It has been recognized that there are inherent survival differences between males and females (i.e., females have a longer life expectancy). However, we found that males with SSc have increased mortality above that which is observed for males in the general population. Our cause-of-death data were limited, precluding in-depth analysis of sex differences in cause-specific mortality. However, general inspection of the data did not reveal any evident differences between the sexes in cause of death.

Our study found differences between sexes in short-term survival, and as time progressed, the survival differences became greater. When comparing the Kaplan-Meier survival curves, it appears that the survival difference between males and females begins to increase at 5 years of disease activity. Kuo, *et al*[13] found that the mortality risk in dcSSc was higher in males than in females. Mean age at death was significantly lower than that of the Taiwanese national population, and the all-cause standardized mortality ratio was higher in males than in females. Although SSc is more common in women, they found that the mortality risk in males was 1.6 times that of females and a 66.1% increase in mortality risk for every 10-year increase in age at diagnosis. The controversy that lies in this area is that other studies have shown sex to not affect survival rates. Al-Dhaher, *et al*[24] suggested that there was no difference in survival rates between men and women. The sex-specific differences they report were that men had an earlier age of disease onset, greater likelihood of having the diffuse subtype, and earlier average age at death. In our study, accounting for differences in SSc subtype, serology, and presence of ILD, males still had increased mortality compared to females. These findings indicate that males acquire SSc less frequently, but have a poorer prognosis once the disease is diagnosed[3]. In our study, males and females had a comparable age at diagnosis, but males had a shorter disease duration. Sensitivity analyses evaluating the potential effect of age at diagnosis and postmenopausal status found that males still had decreased survival.

Table 3. SSc cause of death by sex.

Characteristics	Female	Male
SSc related		
Cardiac		
Cardiac dysrythmia	1	1
Tamponade	1	0
Respiratory		
Respiratory failure	3	2
Pulmonary hypertension	34	9
Interstitial lung disease	6	4
GI		
Bowel infarction	1	0
Bowel obstruction/perforation	2	0
Pseudomembranous colitis	1	0
Malnutrition	—	1
Upper GI bleed	1	0
Renal failure	16	5
SSc attributed*	2	1
SSc unrelated		
Cancer	19	6
Cardiac		
Congestive heart failure	3	0
Heart failure, cardiomyopathy	2	0
Heart failure, nonspecific	13	2
Myocardial infarction	7	1
Cardiac arrest	4	1
Infection		
Pneumonia	10	2
Sepsis	4	—
Thromboembolic		
Portal vein thrombosis	0	1
Pulmonary emboli	0	0
Other		
Hemorrhagic stroke	1	0
Intraabdominal hemorrhage	1	0
Intracranial bleed	1	0
Ischemic stroke	1	2
Sudden death	1	1
Suicide	3	0

*Cause of death attributed to SSc, but not further specified. SSc: systemic sclerosis; GI: gastrointestinal.

Various etiologies have been hypothesized to explain the female predominance of SSc, while also explaining the worse prognosis seen in males. Factors may include immunological considerations, sex-specific environmental exposure, or reproductive aspects, such as skewed X chromosome inactivation[14,19,45]. Sex-related factors such as estrogen may amplify the initiating trigger for the disease, whereas genetic factors may affect disease severity[14]. In addition, sex differences affect drug action, and it has been suggested that therapy specifically tailored to men and women should be developed. Another hypothesis is that males may be less likely to seek medical attention which may lead to presentation with more advanced disease[9].

The sex chromosome hypothesis supports the idea that the X chromosome has genes important for sex hormone levels and immunologically relevant genes[11]. Females are functional mosaics for X-linked genes as a consequence of random X chromosome inactivation[57]. Skewed X inactivation may occur because of a selective advantage between cell groups in a mosaic female[58,59]. About 10% of females have skewing such that greater than 95% of their cells express the same parental allele. Skewing that favors the mutant gene will increase the manifestations. Ozbalkan, *et al* found that nearly half of a group of 55 females with SSc have extremely skewed X inactivation in their blood cells[60].

Our findings suggest that males have a worse survival rate than females, despite a modest increase in disease prevalence. The strengths of our study are the large number of patients, the length of time over which patients were followed, and comparison to the general population. A limitation of our study is that it was underpowered to detect statistical significance in small differences in clinical manifestations. These differences, however, may be clinically significant both in isolation and together. There may also be a selection bias toward more severe disease and those with PAH because we are a quaternary academic center and affiliated with a large pulmonary HTN program. At our center, nailfold capillaries are evaluated systematically by visual inspection (not using assistive devices) and SSc-specific antibodies were not easily available in the early decades of our cohort. This would not affect the internal validity of our findings, because there was no difference in data collection between males and females. However, our findings may reflect an underestimation of nailfold abnormalities and SSc antibodies, and an overrepresentation of pulmonary HTN. This may affect comparison of our results to other SSc centers. For our study, we chose time 0 for the survival analysis as "time from diagnosis" because we could then be more precise about the starting date (less susceptible to recall bias), apply it uniformly to the cohort, and be sure that the patient had the diagnosis of SSc. This may have biased our results to shorter disease durations than would have been estimated using time of onset of Raynaud or first non-Raynaud phenomenon. Our cause-of-death data are limited and we did not have access to death certificate data. Our cause-of-death data came from the hospital or patient charts. It has been suggested that cause of death obtained from death certificates is a less valid data source compared to patient charts[61]. Therefore, despite there being less available data, we can be more certain of data accuracy. There was no difference between sexes in loss to followup. Finally, our primary outcome of all-cause mortality is strong, so this would not systematically bias our findings.

Our findings justify the need for research to further understand the mechanisms and implications of sex-based disparities in SSc. The next phase of research should investigate sex-based differences in comorbid disease, health-seeking behaviors, and access and response to medications. Clinical researchers should be aware of the sex-based disparities in manifestations and survival. If

Table 4. Summary of published literature: characteristics and survival among males and females with systemic sclerosis (SSc).

Study	Sample Size, n (% Female)	Mean Age, yrs, Male/Female	1-yr Survival (%)		3-yr Survival (%)		5-yr Survival (%)		10-yr Survival (%)	
			M	F	M	F	M	F	M	F
Czirjak 2008[10]	366 (86)	56.8	NA		NA		78.3	84.9	66	73.6
Bryan 1999[54]	280 (77)	47.3/45.2	NA		NA		32	26	NA	
Al-Dhaher 2010[24]	185 (85)	52.1/58.9	NA		NA		91	90	82	81
Medsger 1973[15]	358 (M)	48.7 (M)	NA		NA		44 (M)		35 (M), 7-yr survival	
Medsger 1971[3]	Pittsburgh 223 (63), Memphis 86 (60)	Pittsburgh 46.8 yrs, Memphis 48.3 yrs	68 cumulative*				48 cumulative*		35 7-yr survival rate*	
			(< 45): 89, (45 +): 73	(< 45): 97, (45 +): 88	(< 45): 76, (45 +): 54	(<45): 90, (45 +): 47	(< 45): 67, (45 +): 43	(< 45): 86, (45 +): 66	(< 45): 67, (45 +): 34	(< 45): 80, (45 +): 47
Bennett 1971[31]	67 (84)	46.2	NA		NA		< age 40: 95, > age 40: 50		< age 40: 70, > age 40: 30	
Hesselstrand 1998[11]	249	49.4	NA		NA		61	90	40	52
Hashimoto 2011[49]	405 (93)	47	NA		NA		NA		72.5	88.7
Panopoulos 2013[55]	231 (87)	45.7/45.9	NA		85.7	98.8	77.2	97.3**	64.3	92.4***

*White patients with SSc without organ involvement. **6-year survival. ***9-year survival. NA: not available.

Table 5. Summary of published literature: differences in disease manifestations between males and females with systemic sclerosis. All values are males (%) vs females (%) unless otherwise specified.

Study	Myositis	Scleroderma Renal Crisis	PAH	ILD	RP	Serology
Simeon 1996[53]	44 vs 6	11 vs 9	55 vs 72*	NA	NA	NA
Al-Dhaher 2010[24]	NA	16 vs 6	36 vs 28	22 vs 13	NA	ANA-positive, 42 vs 62
Nguyen 2011[46]	NA	12.9 vs 8.3	NA	54.8 vs 41.2	95.2 vs 97.8	NA
Krzyszczak 2011[56]						Anti-U3 RNP were found only in females
White	NA	8 vs 15	23 vs 15	46 vs 37	NA	
African	NA	0 vs 5	33 vs 25	67 vs 65	NA	
Panopoulos 2013[55]	NA	17.4 vs 2.9, p = 0.006	18.2 vs 12.6, p = 0.50	No difference, 45.5 vs 40.7, p = 0.68	NA	No difference: Scl-70, 66.7 vs 59.3, p = 0.50; ACA, 9.5 vs 22.8, p = 0.17

*Lung involvement. NA: not available; ANA: antinuclear antibody; ACA: anticentromere antibodies; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; RP: Raynaud phenomenon; Scl-70: topoisomerase.

disproportionate frequencies of males exist between treatment arms of a study, stratification or adjustment by sex may be needed in the analysis[62].

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