

Epidemiology and Survival of Systemic Sclerosis-Systemic Lupus Erythematosus Overlap Syndrome

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ABSTRACT. Objective. Systemic sclerosis (SSc) may overlap with systemic lupus erythematosus (SLE). Little is known about the epidemiology, clinical characteristics, and survival of SSc-SLE overlap. We evaluated the prevalence of SSc-SLE overlap and differences in SSc characteristics, and compared survival with SSc without SLE.

Methods. A cohort study was conducted including subjects who fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for SSc and/or the ACR criteria for SLE. The primary outcome was time from diagnosis to all-cause mortality. Survival was evaluated using Kaplan-Meier and Cox proportional hazard models.

Results. We identified 1252 subjects (SSc: n = 1166, SSc-SLE: n = 86) with an SSc-SLE prevalence of 6.8%. Those with SSc-SLE were younger at diagnosis (37.9 yrs vs 47.9 yrs, $p < 0.001$), more frequently East Asian (5.5% vs 20%) or South Asian (5.1% vs 12%), had lupus anticoagulant (6% vs 0.3%, $p < 0.001$), anticardiolipin antibody (6% vs 0.9%, $p < 0.001$), and pulmonary arterial hypertension (PAH; 52% vs 31%, $p < 0.001$). Those with SSc-SLE less frequently had calcinosis (13% vs 27%, $p = 0.007$), telangiectasia (49% vs 75%, $p < 0.001$), and diffuse subtype (12% vs 35%, $p < 0.001$). There were no significant differences in the occurrence of renal crisis (7% vs 7%), interstitial lung disease (ILD; 41% vs 34%), and digital ulcers (38% vs 32%). Those with SSc-SLE had better median survival time (26.1 vs 22.4 yrs), but this was not statistically significant (log-rank $p = 0.06$). Female sex and diffuse subtype attenuated survival differences between groups (HR 1.07, 95% CI 0.67–1.67).

Conclusion. Patients with SSc-SLE are younger at diagnosis, more frequently have PAH, and less frequently have cutaneous manifestations of SSc. They should be monitored for ILD, renal crisis, and digital ulcers. (First Release July 15 2018; J Rheumatol 2018;45:1406–10; doi:10.3899/jrheum.170953)

Key Indexing Terms:

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Systemic sclerosis (SSc) is an immune disorder characterized by vasculopathy and fibrosis. Women are more frequently affected, with a female-to-male sex ratio of 4.7:1¹. It is the systemic autoimmune rheumatic disease (SARD) with the highest disease-related mortality and morbidity with an impaired health-related quality of life². In some cases, SSc may overlap with another SARD, such as systemic lupus erythematosus (SLE; also called lupoderma)^{3–10}. The prevalence of SSc-SLE overlap syndrome ranges from 8.4% to 14.7%^{11,12,13}. Overlap syndromes can present in both the diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc) subtypes, with a prevalence of 10–38%^{5,6,9–13}.

Little is known about the epidemiology, clinical characteristics, and survival of SSc-SLE overlap syndrome. It has been reported that patients with SSc-SLE overlap syndrome are significantly younger at SSc onset than those with SSc without SLE¹³. Patients with SSc-SLE overlap syndrome presented with Raynaud phenomenon more frequently¹³. Also reported in SSc-SLE overlap are discoid lupus, lupus nephritis, pancreatitis, avascular bone necrosis, and shrinking lung syndrome^{13–19}. Serological markers are relevant in SSc-SLE overlap syndrome because anti-U1RNP was significantly more frequent in patients with SSc-SLE¹¹. Survival in SSc-SLE overlap syndrome has not been reported.

The aim of our study was to evaluate the epidemiology of SSc-SLE overlap syndrome compared to SSc. We evaluated the prevalence of SSc-SLE overlap syndrome and differences in SSc disease manifestations, and compared survival in SSc patients with and without SLE.

MATERIALS AND METHODS

Patients. The Toronto Scleroderma Program, a health network comprising 3 academic hospitals (Toronto Western Hospital, Mount Sinai Hospital, and Toronto General Hospital, Toronto, Ontario, Canada), is the largest single-center longitudinal cohort in Canada. Patients are followed every 6 to 12 months using a standardized protocol. Subjects who fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc²⁰ and were ≥ 16 years of age were included in this cohort study. We excluded subjects with localized scleroderma (morphea). SSc-SLE overlap subjects fulfilled the ACR/EULAR classification criteria for SSc and the ACR classification criteria for SLE with ≥ 4 criteria, or 3 ACR criteria plus a typical histologic lesion of SLE on renal or skin biopsy^{21,22}. For the overlap subjects, time zero was fulfillment of classification criteria for either SSc or SLE. The study period was 1970–2017.

Outcomes. The primary outcome was the time from diagnosis to death from all causes. Subjects who were alive as of January 1, 2017, were censored. A standardized, systematic method of survival status assessment was used²³. Dates of death were obtained from the clinic chart, hospital electronic record, or obituary. If a patient was alive for the last scheduled clinic visit, the family/referring physicians were contacted using a standardized letter. Information about survival status was collected. This approach has been shown to be a valid and reliable method for tracking patients as a source of mortality data²³, and has been successfully used in other research work^{24,25}.

Secondary outcomes included the prevalence of SSc-SLE overlap syndrome, SSc subtype (lcSSc, dcSSc), calcinosis, Raynaud phenomenon, digital ulceration, esophageal dysmotility, 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 thorax²⁵), pulmonary arterial hypertension (PAH; mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg by right heart catheterization)²⁰, renal crisis [acute renal failure, new onset hypertension, normal or mild proteinuria on urinalysis, microangiopathic hemolytic anemia], and serology (topoisomerase, centromere antibodies, anti-dsDNA, anti-Sm, anti-U1RNP). RNA polymerase III antibody was not evaluated because that process is not available at our center.

Statistical analysis. Descriptive statistics, specifically standardized mean difference (SMD) with 95% CI, were used to summarize the clinical and serologic data. A conservative threshold of SMD $> 25\%$ was considered statistically significant, verified with a p value < 0.05 . Subjects who were alive on January 1, 2017, were right-censored. Survival rates for 1–5 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.

Research ethics board approval was obtained for the conduct of this study (REB 16-0318-C). Because of the long duration of followup and high mortality, written consent was waived.

RESULTS

Patients. The study included 1252 subjects (SSc: $n = 1166$, SSc-SLE: $n = 86$). The prevalence of SSc-SLE overlap was 6.8%. SSc-SLE subjects were more frequently female (92% vs 81%, $p = 0.02$) and less frequently had diffuse subtype (12% vs 35%, $p < 0.001$). The mean age at diagnosis of SSc-SLE subjects was significantly younger than SSc subjects without SLE (37.9 vs 47.9 yrs, $p < 0.001$). Compared to SSc subjects, SSc-SLE subjects were more commonly East Asian (5.5% vs 20%) and South Asian (5.1% vs 12%).

Disease manifestations. SSc-SLE overlap subjects more frequently had lupus anticoagulant (LAC; 6% vs 0.3%, SMD 32%, $p < 0.001$), anticardiolipin antibodies (aCL; 6% vs 0.9%, SMD 27%, $p < 0.001$), and PAH (52% vs 31%, SMD 44%, $p < 0.001$), and less frequently had calcinosis (13% vs 27%, SMD 35%, $p = 0.007$) and telangiectasia (49% vs 75%, SMD 56%, $p < 0.001$). There were no significant differences in the occurrence of renal crisis (7% vs 7%, SMD 2%), ILD (41% vs 34%, SMD 14%), and digital ulcers (38% versus 32%, SMD 12%; Table 1). In terms of comorbidities, there were no significant differences in the occurrence of hypertension (19% vs 21%), diabetes (6% vs 6%), dyslipidemia (5% vs 7%), or cancer (7% vs 11%) between groups (Table 2). All the SSc-SLE subjects had anti-dsDNA or anti-Sm antibodies.

Survival. There were 432 deaths (SSc: $n = 411$, SSc-SLE:

Table 1. Comparison of disease manifestations between SSc-SLE and SSc subjects.

Disease Manifestations	SSc, n (%)	SSc-SLE overlap, n (%)	SMD*, %
Calcinosis	310 (27)	11 (13)	35
Raynaud phenomenon	1110 (95)	80 (93)	9
Esophageal dysmotility	1005 (86)	67 (78)	22
Sclerodactyly	1095 (94)	57 (66)	74
Telangiectasia	877 (75)	42 (49)	56
Interstitial lung disease	396 (34)	35 (41)	14
Pulmonary arterial hypertension	362 (31)	45 (52)	44
Scleroderma renal crisis	76 (7)	6 (7)	2
Abnormal nailfold capillaries	370 (32)	27 (31)	0.7
Digital ulcers	378 (32)	33 (38)	12
Scl-70 antibody	202 (17)	10 (12)	16
Centromere antibody	229 (20)	12 (14)	15
Lupus anticoagulant	4 (0.3)	5 (6)	32
Anticardiolipin antibody	11 (0.9)	5 (6)	27

* SMD $> 25\%$ is considered a meaningful difference between groups. SSc: systemic sclerosis; SLE: systemic lupus erythematosus; SMD: standardized mean difference.

Table 2. Comparison of comorbidities between SSc-SLE and SSc subjects.

Comorbidities	SSc, n (%)	SSc-SLE overlap, n (%)	SMD*, %
Coronary artery disease	104 (9)	3 (4)	23
Hypertension	244 (21)	16 (19)	6
Diabetes mellitus	66 (6)	5 (6)	0.7
Dyslipidemia	84 (7)	4 (5)	11
Peripheral vascular disease	46 (4)	4 (5)	3
Cancer	128 (11)	6 (7)	14
Stroke	30 (3)	2 (2)	2
Atrial fibrillation	47 (4)	4 (5)	3

* SMD > 25% is considered a meaningful difference between groups. SSc: systemic sclerosis; SLE: systemic lupus erythematosus; SMD: standardized mean difference.

n = 21). The Kaplan-Meier curves suggest that SSc-SLE overlap subjects have similar survival (log-rank p = 0.06). The median survival time for SSc-SLE subjects was 26.1 years and SSc was 22.4 years (Figure 1). Although the cause

of death in the SSc-SLE group was largely unknown (n = 79), known causes of death included heart failure (n = 2), sepsis (n = 2), bowel obstruction (n = 1), pulmonary embolism (n = 1), and myocardial infarction (n = 1).

Cox proportional hazard models adjusting for female sex, diffuse subtype, LAC, aCL, pulmonary hypertension, and age at diagnosis demonstrated no significant difference between the 2 groups (HR 1.07, 95% CI 0.67–1.67). The difference in survival in the unadjusted analysis was attenuated when diffuse type and female sex were controlled in the model (Table 3).

DISCUSSION

In our study, we evaluated the epidemiology of SSc-SLE overlap compared to SSc. Few studies have evaluated its prevalence and clinical characteristics, and we found no studies that evaluated the survival difference in SSc-SLE overlap compared to SSc. To our knowledge, this is the largest study to evaluate the epidemiology of SSc-SLE in the

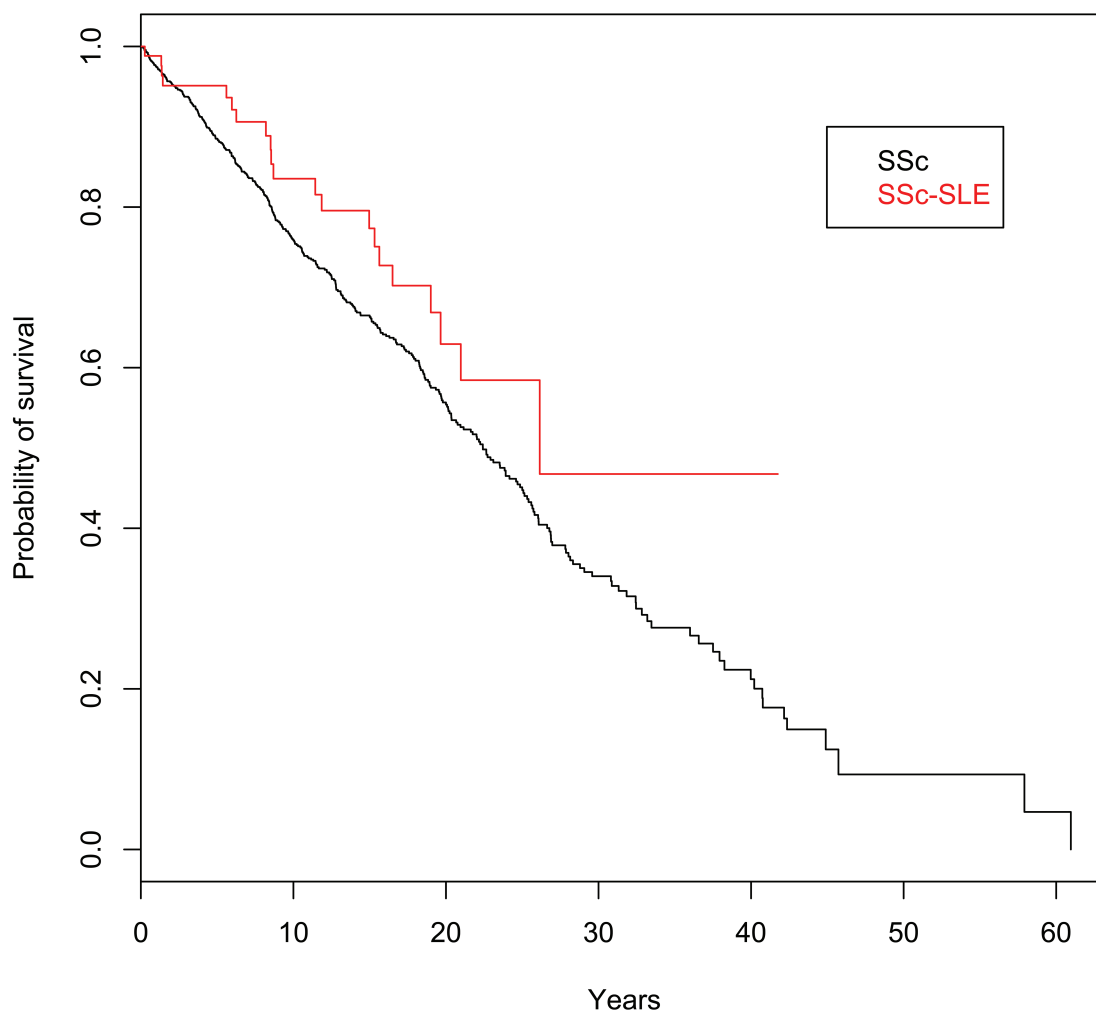


Figure 1. Kaplan-Meier curves comparing survival between SSc-SLE and SSc subjects. SSc: systemic sclerosis; SLE: systemic lupus erythematosus.

Table 3. Comparison of short-term, longterm, and median survival between SSc-SLE and SSc subjects. Values are % (95% CI) unless otherwise specified.

Probability of Survival, Yrs	SSc	SSc-SLE Overlap
5	88.5 (86.6–90.5)	95.1 (90.6–99.9)
10	75.8 (73.1–78.7)	83.5 (74.9–93.1)
15	66.5 (63.2–70)	77.3 (67.3–88.9)
20	55.4 (51.5–59.6)	62.9 (49.8–80)
Median survival time	22.4	26.1

SSc: systemic sclerosis; SLE: systemic lupus erythematosus.

modern era and the first to use the ACR/EULAR classification criteria for SSc in these overlap patients.

The prevalence of SSc-SLE overlap in our cohort was 6.8%, which suggests that SSc-SLE overlap is not uncommon among patients with SSc. This is similar but slightly lower than what was reported in other studies^{12,14}. We demonstrated that SSc-SLE subjects are more frequently female, which validates a similar finding¹⁴. We also demonstrated that patients with SSc-SLE have a younger age at diagnosis, and are more commonly South or East Asian.

In our study, SSc-SLE overlap subjects less frequently had cutaneous manifestations of SSc, notably diffuse skin involvement, calcinosis cutis, and telangiectasia. We found that SSc-SLE subjects more frequently had pulmonary hypertension. The frequency of pulmonary hypertension among SSc-SLE overlap subjects has been varied. In 1 cohort with 11 subjects who had SSc-SLE, none of them had pulmonary hypertension¹¹. In another study that identified 2 subjects with SSc-SLE overlap, both of them had pulmonary hypertension⁶.

We also found that the other severe manifestations of SSc (renal crisis, ILD, and digital ulcers) occur with similar frequency in both SSc-SLE and SSc subjects. Interestingly, despite SSc-SLE subjects less frequently having diffuse cutaneous involvement, the frequency of ILD was similar between groups. Indeed, ILD can occur in SLE, but it may be that the presence of concomitant SSc increases the risk of ILD in subjects with SLE. This suggests that SSc-SLE subjects should routinely be monitored for pulmonary hypertension, ILD, renal crisis, and digital ulcers.

Our study identified that SSc-SLE subjects more frequently had LAC (6% vs 0.3%, $p < 0.001$) and aCL (6% vs 0.9%, $p < 0.001$). Previous studies have identified a correlation between aCL and/or LAC and increased risk of vascular impairment in SSc¹. The presence of antiphospholipid antibodies increases the risk of PAH, digital infarcts, angina pectoris, and myocardial infarction^{26,27,28,29}. Assessment of antiphospholipid antibodies in SSc may be warranted because these patients may require close monitoring of vascular changes, in particular PAH and digital infarcts. We also demonstrated that comorbid illnesses of hypertension,

diabetes mellitus, dyslipidemia, and cancer occur with equal frequency in both SSc-SLE and SSc.

Finally, we evaluated survival in SSc subjects with and without SLE. Unadjusted survival analysis suggests that SSc-SLE overlap subjects have similar survival. Accounting for female sex, age at diagnosis, and diffuse subtype reduced the perceived survival differences between the 2 groups. It appears that having an overlap with SLE does not confer either an increased risk or protective effect for mortality.

A potential limitation of our study is that our prevalence estimate may be conservative because we required all subjects to fulfill the classification criteria for SSc and SLE to be included. We may have missed cases of mild or early disease where the subject has a physician-based diagnosis but does not fulfill the classification criteria^{30,31}. However, the standardization of case ascertainment was necessary to facilitate comparisons across future studies³². Our results may also be affected by a survival bias, that is, SSc patients may have died before they developed SLE. Alternatively, it is possible that SLE features may bring a diagnosis of SSc to light earlier, noting the younger age and less sclerodactyly in these subjects. The proportion of patients with SSc antibodies appears low, because measurement of SSc-specific antibodies was not readily available in the early decades of our cohort. Our center is a tertiary PAH referral center, and this may have resulted in the high prevalence of PAH in both the SSc and SLE-SSc groups. Strengths of our study include our long followup time, large sample size (for rare diseases), and robust mortality data.

In this large, well-characterized cohort study with robust mortality data, we demonstrated that SSc-SLE overlap is not uncommon among those with SSc. SSc-SLE subjects are more frequently female, have a younger age at diagnosis, and less frequently have cutaneous manifestations of SSc. However, these subjects should be monitored for serious complications of SSc, including pulmonary hypertension, ILD, renal crisis, and digital ulcers.

REFERENCES

- Hussein H, Lee P, Chau C, Johnson SR. The effect of male sex on survival in systemic sclerosis. *J Rheumatol* 2014;41:2193-200.
- Almeida C, Almeida I, Vasconcelos C. Quality of life in systemic sclerosis. *Autoimmun Rev* 2015;14:1087-96.
- Pope JE. Scleroderma overlap syndromes. *Curr Opin Rheumatol* 2002;14:704-10.
- Fiori G, Pignone A, Cerinic MM. Overlap syndromes. *Reumatizam* 2002;49:12-5.
- Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis at the crossroad of polyautoimmunity. *Autoimmun Rev* 2013;12:1052-7.
- Balbir-Gurman A, Braun-Moscovici Y. Scleroderma overlap syndrome. *Isr Med Assoc J* 2011;13:14-20.
- Wutzl AL, Foley RN, O'Driscoll BR, Reeve RS, Chisholm R, Herrick AL. Microscopic polyangiitis presenting as pulmonary-renal syndrome in a patient with long-standing diffuse cutaneous systemic sclerosis and antibodies to myeloperoxidase. *Arthritis Rheum* 2001;45:533-6.
- Zandman-Goddard G, Tweezer-Zaks N, Shalev T, Levy Y, Ehrenfeld

- M, Langevitz P. A novel overlap syndrome: systemic sclerosis associated with antiphospholipid syndrome—a case series. *Ann N Y Acad Sci* 2007;1108:497-504.
9. Caramaschi P, Biasi D, Volpe A, Carletto A, Cecchetto M, Bambara LM. Coexistence of systemic sclerosis with other autoimmune diseases. *Rheumatol Int* 2007;27:407-10.
 10. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, et al; Registry of the German Network for Systemic Scleroderma. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. *Rheumatology* 2008;47:1185-92.
 11. Pakozdi A, Nihtyanova S, Moinzadeh P, Ong VH, Black CM, Denton CP. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. *J Rheumatol* 2011;38:2406-9.
 12. Moinzadeh P, Aberer E, Ahmadi-Simab K, Blank N, Distler JH, Fierlbeck G, et al. Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2015;74:730-7.
 13. Foocharoen C, Netwjitpan S, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Clinical characteristics of scleroderma overlap syndromes: comparisons with pure scleroderma. *Int J Rheum Dis* 2016;19:913-23.
 14. Suzuki Y, Okamoto H, Koizumi K, Tateishi M, Hara M, Kamatani N. A case of severe acute pancreatitis, in overlap syndrome of systemic sclerosis and systemic lupus erythematosus, successfully treated with plasmapheresis. *Mod Rheumatol* 2006;16:172-5.
 15. Guleria VS, Singh PK, Saxena P, Subramanian S. Shrinking lung syndrome in systemic lupus erythematosus-scleroderma overlap. *Lung India* 2014;31:407-9.
 16. Cavallasca JA, Laborde HA, Araujo MB, Nasswetter GG. Multiple avascular necrosis in a patient with systemic lupus erythematosus/systemic sclerosis overlap syndrome. *Clin Rheumatol* 2005;24:406-8.
 17. Umbert P, Winkelmann RK. Concurrent localized scleroderma and discoid lupus erythematosus. Cutaneous 'mixed' or 'overlap' syndrome. *Arch Dermatol* 1978;114:1473-8.
 18. Sasaki T, Nakajima H. Systemic sclerosis (scleroderma) associated with discoid lupus erythematosus. *Dermatology* 1993;187:178-81.
 19. Bhansing KJ, Lammens M, Knaapen HK, van Riel PL, van Engelen BG, Vonk MC. Scleroderma-polymyositis overlap syndrome versus idiopathic polymyositis and systemic sclerosis: a descriptive study on clinical features and myopathology. *Arthritis Res Ther* 2014;16:R111.
 20. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72:1747-55.
 21. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
 22. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
 23. Soowamber ML, Granton JT, Bavaghar-Zaeimi F, Johnson SR. Online obituaries are a reliable and valid source of mortality data. *J Clin Epidemiol* 2016;79:167-8.
 24. Rosenthal AK, McLaughlin JK, Gridley G, Nyren O. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995;76:910-4.
 25. Johnson SR, Granton JT, Tomlinson GA, Grosbein HA, Le T, Lee P, et al. Warfarin in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. A Bayesian approach to evaluating treatment for uncommon disease. *J Rheumatol* 2012;39:276-85.
 26. Marie I, Jouen F, Hellot MF, Levesque H. Anticardiolipin and anti-beta2 glycoprotein I antibodies and lupus-like anticoagulant: prevalence and significance in systemic sclerosis. *Br J Dermatol* 2008;158:141-4.
 27. Picillo U, Migliaresi S, Marcialis MR, Ferruzzi AM, Tirri G. Clinical significance of anticardiolipin antibodies in patients with systemic sclerosis. *Autoimmunity* 1995;20:1-7.
 28. Assou N, Allanore Y, Batteux F, Meune C, Toulon P, Weill B, et al. Prevalence of antiphospholipid antibodies in systemic sclerosis and association with primitive pulmonary arterial hypertension and endothelial injury. *Clin Exp Rheumatol* 2005;23:199-204.
 29. Morrisroe KB, Stevens W, Nandurkar H, Prior D, Thakkar V, Roddy J, et al. The association of antiphospholipid antibodies with cardiopulmonary manifestations of systemic sclerosis. *Clin Exp Rheumatol* 2014;32:S133-7.
 30. Johnson S, Khanna D, Allanore Y, Matucci-Cerinic M, Furst D. Systemic sclerosis trial design moving forward. *J Scleroderma Relat Disord* 2016;1:177-80.
 31. Johnson SR. New ACR EULAR guidelines for systemic sclerosis classification. *Curr Rheumatol Rep* 2015;17:32.
 32. Johnson SR, Goek ON, Singh-Grewal D, Vlad SC, Feldman BM, Felson DT, et al. Classification criteria in rheumatic diseases: a review of methodologic properties. *Arthritis Rheum* 2007;57:1119-33.