RHEUMATOLOGY

Rheumatology 2010;49:1112–1117
doi:10.1093/rheumatology/keq046
Advance Access publication 11 March 2010

Original article

Age-related survival and clinical features in systemic sclerosis patients older or younger than 65 at diagnosis

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Abstract

Objective. To analyse the differences in SSc clinical features and survival in patients aged ⩾65 years compared with young SSc patients.

Methods. Of a total of 319 SSc patients, we identified 67 (21%) patients aged >65 years. Demographical data such as SSc subsets, the cutaneous complaint, internal organ involvement and the causes of morbidity and mortality were collected. Results of the elderly and young patients were compared.

Results. There were 61 (91%) women and 6 (9%) men aged ⩾65 years. The limited SSc (lSSc) subset was more prevalent in elderly than in young patients (74.6 *vs* 54%, $P = 0.002$). Pulmonary disease (86.6% in elderly *vs* 73.8% in young patients, $P = 0.034$) and cardiac involvement (70.1% in elderly *vs* 49.6% in young patients, $P = 0.004$) were significantly more prevalent in elderly patients. In contrast, signs of oesophageal involvement (43.3% in elderly *vs* 57.5% in young patients, $P = 0.040$) were less frequent in aged patients. In addition, pulmonary and heart disease appeared significantly earlier after the diagnosis in patients aged ⩾65 years. Mortality was significantly higher in elderly than in young patients (35.8 *vs* 19%, $P = 0.005$), but when standardized mortality ratios (SMRs) were analysed, there was no significant mortality increase in the elderly.

Conclusion. In elderly patients, the lSSc subset is more prevalent than the diffuse. Pulmonary and cardiac involvement are more prevalent in aged patients and appears sooner after the disease diagnosis. SSc is clearly related to increased mortality, although it is not significant in the elderly group.

Key words: Systemic sclerosis, Elderly, Visceral involvement, Mortality, Survival.

CLINICAL SCIENCE

Introduction

SSc is a rare and life-threatening autoimmune disease of unknown origin. Fibrosis is the final stage in a series of pathological events that begins with vascular dysfunction, endothelial activation and oxidative stress, followed by immunological activation, extravascular inflammation and fibroblasts activation [1–3]. All studies show a female excess varying from 2 : 1 to 8 : 1, and the disease more commonly occurs in the fifth decade of life, although it is also described in both young and elderly patients [4].

SSc affects not only the skin but also a variety of organ systems, notably the musculoskeletal, renal, pulmonary, cardiac and gastrointestinal systems. The diagnosis of SSc is suggested by the presence of cutaneous sclerosis in more than one area and supported by the presence of internal organ involvement, characteristic autoantibodies and typical nail-fold capillaroscopic features [5–8]. The extent of skin involvement constitutes the basis for classification of SSc [5–7, 9, 10]. The ARA published the classification criteria in 1980 [5]. The classification of SSc subsets is important to organ involvement and survival prognostics [11, 12]. There are some studies reporting from 34 to 73% survival of SSc patients 5 years after

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Submitted 24 October 2009; revised version accepted 27 January 2010.

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diagnosis [11–13]. The mortality rate is increased in SSc patients compared with an age- and sex-matched population as was previously described in our series of patients, with a 4-fold increase in mortality [12].

Ageing is a process that converts healthy adults into frail ones, with diminished reserves in most physiological systems and exponentially increasing vulnerability to most diseases, leading to death [14]. Some observational studies have demonstrated that ageing modifies the clinical and serological phenotype of several autoimmune disorders, including SLE, RA, inflamatory myositis, SS and SSc [15–20].

SSc has been well described in elderly patients, and some clinical differences between elderly and young patients with SSc have been reported [4, 19, 21], although there are no studies about the incidence of SSc in aged patients.

The aim of our study was to analyse the clinical characteristics of SSc patients diagnosed after the age of 65 years at our institution, and to evaluate the differences between elderly ($\geqslant$65 years) and young SSc patients related to clinical presentation and survival.

Patients and methods

We reviewed the medical records of 319 patients diagnosed between 1976 and 2007 as having SSc and followed up at our department. We identified 67 (21%) of them who were diagnosed with SSc after the age of 65 years. Disease onset was defined as the self-reported date of the first symptom (RP in the majority of patients), and SSc diagnosis date was considered when the patient accomplished the ARA criteria [5]. A standardized clinical protocol was filled in for each patient and appropriate complementary tests were requested. The following demographical data were collected: age, gender and age at diagnosis, first manifestation (usually RP) and systemic manifestation developments. We also recorded the SSc subsets, the cutaneous complaint, the involvement of internal organs and the time between SSc diagnosis and each manifestation development, as well as the causes of morbidity and mortality. The criteria for evaluating the manifestations of SSc are detailed below.

Clinical features

Skin involvement. Four separate groups of SSc patients were established: diffuse SSc (dSSc), including patients with sclerosis distal and proximal to the elbows and knees; limited SSc (lSSc), including patients with sclerosis only distal to elbows and knees; scleroderma sine, scleroderma with visceral involvement [pulmonary fibrosis, pulmonary arterial hypertension (PAH) and gastrointestinal] without skin sclerosis; and pre-scleroderma, with immunological and nail-fold capillaroscopy abnormalities, but no clinical manifestations [6, 7, 10].

Digestive tract involvement. Digestive tract involvement secondary to SSc was defined as hypomotility of the lower two-thirds of the oesophagus and/or decreased peristalsis confirmed by manometry in all patients. Intestinal manifestations (diarrhoea and malabsorption syndrome) were also registered, and a breath test was performed when alterations were detected.

Pulmonary involvement. Pulmonary involvement was established when pulmonary interstitial fibrosis or PAH were found. Pulmonary fibrosis was defined on the basis of the following criteria: (i) restrictive pulmonary pattern on pulmonary function tests; and (ii) radiological evidence of interstitial lung disease (ILD) by chest radiograph or CT scan. PAH was detected by Doppler echocardiogram [systolic pulmonary arterial pressure (sPAP) $>$ 40 mmHg] [22, 23] or by catheterization (mean PAP $>$ 25 mmHg). Echocardiogram was performed in all patients, and 23 patients underwent right heart catheterization, 5 of them aged $>$65 years.

Cardiac involvement. Cardiac involvement was established by one or more of the following: clinical symptoms, reversible thallium perfusion defects after cold stimulation [24], any change on colour-Doppler echocardiography, electrocardiographic alterations, left ventricular ejection fraction $<$50% or right ventricular ejection fraction $<$40% on radionuclide ventriculography.

Renal involvement. Renal involvement secondary to SSc was diagnosed when increased serum creatinine concentration or abnormal urine analysis (haematuria, proteinuria $>$500 mg/24 h) were detected in the absence of any other known cause or when a sclerodermic renal crisis (SRC), as defined according to Traub *et al.* [25], was noted.

Nail-fold capillaroscopy. Nail-fold capillaroscopy was performed on each finger of both hands with Wild M3 stereomicroscopy and Intralux 5000 Volpi. According to Maricq *et al.* [8], two capillaroscopic patterns were distinguished: an active pattern characterized by predominance of capillary loss and a slow pattern characterized by megacapillaries with no capillary loss.

Laboratory analysis

A complete blood exam was performed with general haematological and biochemical parameters. Autoantibody studies, including ANAs determined by indirect IF technique with Hep-2 cell substrate, ACA and anti-topo I (anti-Scl-70), were determined by immunoblotting; anti-Ro, anti-La, anti-cardiolipine, anti-Sm and anti-RNP, and RF were also determined.

Statistical analysis

The statistical processing of the study was performed using the SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). Comparison of categorical variables was carried out by means of the Fisher's exact test. Subgroup differences of continuous variables were compared with the non-parametric Mann–Whitney U-test. Survival curves were plotted with the Kaplan–Meier method, subgroup differences in survival (elderly *vs* young) have been analysed with the log rank (Mantel–Cox) test. Statistical significance was defined as $P \leqslant 0.05$. The 2006 mortality data

from Catalonia were used to estimate the standardized mortality ratio (SMR) and 95% CIs by a person-years at risk method using the program PAMCOMP 1.41 [26].

Results

Sixty-seven patients aged ⩾65 years were evaluated in our study. The mean age at SSc diagnosis was 71.7 years (range 65–98). There were 61 (91%) women and 6 (9%) men. The SSc subsets are recorded in Table 1. RP was the first symptom in 64 (95.5%) patients. The time between RP beginning and SSc diagnosis was, on average, 10.7 years (S.D. 12.6; range −0.34 to 56.5). Twenty-seven (40.3%) patients aged ⩾65 years had ischaemic cutaneous fingertip ulcers, 50 (74.6%) had telangiectasias and 9 (13.4%) had calcinosis. Extracutaneous organ involvement is reported in Table 1.

Sixty-two (92.5%) patients aged >65 years at diagnosis had ANAs, 34 (58.6%) with speckled pattern, 13 (22.4%) with a centromeric pattern, 6 (10.3%) with a homogeneous pattern and 5 (8.6%) with a nucleolar pattern. ANAs were present in 28 (45.2%) patients and anti-Scl-70 in 6 (10.2%) (Table 1).

Twenty-four patients (35.8%) died during the follow-up. The causes of these deaths were as follows: heart failure in nine patients, pulmonary SSc involvement in eight patients (pulmonary hypertension in five, pulmonary fibrosis in two and both in one patient), renal disease in two cases, ischaemic heart disease in one and malignant disease in another. When we compared elderly with young patients, we found significant differences related to SSc subsets (Table 1), with higher frequency of the limited form in the older group. The time between the first manifestation and the disease diagnosis was not significantly different in either group. RP was present in 98.5% of elderly *vs* 90.5% of young patients ($P = 0.037$). There were no statistically significant differences in cutaneous telangiectasias, calcinosis or fingertip ulcers between both groups according to age. Differences related to the internal organ involvement are reflected in Table 1.

The mean sPAP was 42.6 (20.4) mmHg in young and 53.5 (24.4) mmHg in elderly patients ($P = 0.002$). The ILD resulted in a statistically significant difference in elderly SSc patients *vs* young patients, but when we revised the lung involvement taking into account the forced vital capacity (FVC) ⩽70% or >70%, there were no significant differences between elderly and young patients—FVC ⩽70% in 52 (25.9%) patients aged <65 years and in 21 (38.2%) aged ⩾65 years.

When we analysed the mean time between the different systemic manifestation developments and SSc diagnosis in both groups, we found that all systemic manifestations appear earlier in elderly patients (Table 2). We also reviewed if there were differences in the beginning of systemic manifestations in the first 6 months after the disease diagnosis. In this sense, ILD appeared significantly earlier in elderly patients [$P = 0.001$; 15 (22.4%) *vs* 17 (6.7%)]. We also found a significant difference in pulmonary hypertension ($P = 0.003$). Thus, nine (13.4%) patients in the elderly group developed PAH *vs* eight (3.2%) in the younger group. Heart manifestations also appeared in 24 (35.8%) elderly *vs* 37 (14.7%) young patients ($P \leqslant 0.0005$) in the first 6 months after disease diagnosis. Temporal differences were not found to be significant in SRC nor in gastrointestinal involvement.

No significant differences were found related to nail-fold capillaroscopic pattern between both groups of patients. Forty-two patients (75%) aged ⩾65 years had a slow pattern, whereas nine (16.1%) had an active pattern and five (8.9%) had an unspecific or normal capillaroscopic pattern.

Table 1 Main Clinical features

	⩾65 years (*n* = 67), *n* (%)	<65 years (*n* = 252), *n* (%)	*P*-value
SSc subsets			
lSSc	50 (74.6)	136 (54)	
dSSc	5 (7.5)	59 (23.4)	
SSc sine	11 (16.4)	34 (13.5)	
Pre-scleroderma	1 (1.5)	23 (9.1)	0.002
Systemic affections			
Musculoskeletal	40 (59.7)	180 (71.4)	0.075
Gastrointestinal	45 (67.2)	190 (75.4)	0.211
Oesophageal	29 (43.3)	145 (57.5)	0.040
Pulmonary	58 (86.6)	186 (73.8)	0.034
ILD	43 (64.2)	108 (42.9)	0.002
PAH	19 (28.4)	42 (16.7)	0.036
Cardiac	47 (70.1)	125 (49.6)	0.004
CSD[a]	21 (31.3)	46 (18.3)	0.027
Renal	4 (6)	17 (6.7)	1.000
Sicca syndrome	25 (37.3)	52 (20.6)	0.006
Cancer	7 (10.4)	14 (5.6)	0.167
Immunological features			
ANAs	62 (92.5)	244 (96.8)	0.156
Anti-centromere	28 (45.2)	99 (41.8)	0.666
Anti-Scl70	6 (10.2)	49 (21.3)	0.062
Disease duration, years[b]	6.91 (5.56)	11.03 (7.48)	

[a]CSD: conduction system disease; [b]time between onset of RP and SSc diagnosis (S.D.).

Table 2 Time (years) between SSc diagnosis and systemic involvement development

Systemic involvement	<65 years	⩾65 years
ILD	8.16 (7.4)	3.80 (4.2)
PAH	8.09 (7.2)	1.60 (3.1)
Renal crisis	3.54 (4.8)	1.00 (1.5)
Gastrointestinal	1.61 (4.6)	−0.77 (3.7)
Heart	6.14 (7.0)	2.01 (3.3)

Values are expressed as mean (S.D.).

Regarding immunological features, described in Table 1, we only found differences but not statistically significant in the presence of anti-Scl70 (anti-topol) (10.2 *vs* 21.3%; $P = 0.062$). The median follow-up period was 17.7 (12.3) years for patients aged <65 years and 13.2 (13.1) years for elderly patients ($P = 0.161$).

The deaths in the follow-up period were significantly different between elderly and young subgroups: 35.8 *vs* 19% ($P = 0.005$). The death causes were also statistically different ($P = 0.001$).

The median survival time from diagnosis was 26.5 years among the overall sample. The Kaplan–Meier survival curves were significantly different ($P \leqslant 0.0005$) for both groups of patients (Fig. 1), with a median survival time of 35.6 years in patients <65 years and 12.3 years in the elderly subjects. The accumulated survival ratios are expressed in Table 3.

The SMR of the SSc cohort was 1.9 (1.5–2.3) compared with the background population [26]. Results for the SMR related to age, sex and SSc subsets are shown in Table 4.

Discussion

To our knowledge, this is the most extensive series of elderly SSc patients reported in literature. In a large cohort of 319 patients, diagnosed and followed up at a single institution (Systemic diseases Unit of an Internal Medicine Department), we found 67 patients who were diagnosed with SSc after the age of 65 years. It accounts for 21% of all SSc patients.

The incidence of SSc in elderly is unknown. We have found only one study [27] that dealt with this subject. The author revised 15 SSc cases seen by one physician in geriatric medicine in 11 years, representing an incidence of about 1 per 1000 elderly patients. He suggested that the diagnosis of SSc may be overlooked in elderly patients, due to the minor nature of the skin changes and the best favourable course. To date, few reports of SSc development in elderly patients have been published. In 1971, Medsger found that 14% of his SSc patients were diagnosed after the age of 65 years [28]. Similarly, Laing, in his 1997 study of women with SSc, reported that 2.7% were diagnosed after the age of 75 years [29]. In 2006, Derk described 13 (1.7%) of 769 patients diagnosed with SSc after the age of 75 years [19].

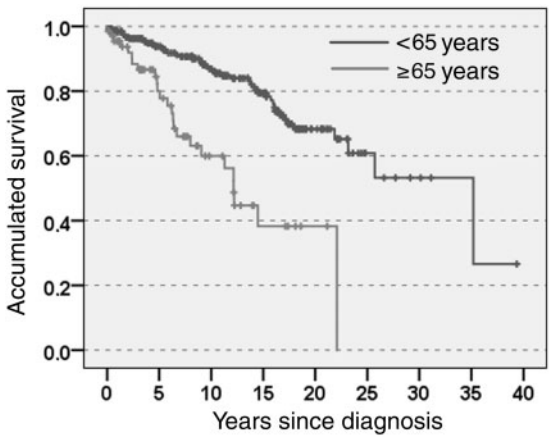
All the reported studies show a female excess (3 : 1 to 7 : 1) with a lesser difference in the fifth and subsequent decades (2–3 : 1) [4, 28]. We found in our series that the female excess remained in the elderly group (9 : 1).

The first manifestation of the disease is RP [9]. In our SSc patients, 98.5% of patients diagnosed after the age of 65 years and 90.5% < 65 years had RP as the first symptom. Digital ulcers or infarction were less frequent in elderly *vs* young patients (40.3 *vs* 52%). The mean time between RP beginning and SSc diagnosis was not different in both groups, despite the minor skin changes in the elderly.

Regarding SSc subsets, we found significant differences related to age, the limited form being more frequent in elderly patients. Some studies have suggested that lSSc is the more frequent subset in elderly patients, but this has not been confirmed in other studies [19].

There are some differences in internal organ involvement according to age, mainly related to pulmonary disease [19–21]. In our patients, our results were similar to those previously reported [9, 19, 30], pulmonary disease was present in 244 (76.49%) patients and in 58 (86.6%) of

Fig. 1 Long-term survival in SSc patients older or younger than 65 years at diagnosis.



Differences in survival between SSc patients older and younger than 65 years.

Table 3 SSc accumulated survival

Years[a]	<65 years	⩾65 years	Total
5	0.92	0.80	0.89
10	0.85	0.64	0.81
15	0.77	0.42	0.71
20	0.68	0.42	0.63

[a]Years since diagnosis.

Table 4 SMR

	Expected no. of deaths	Observed no. of deaths	SMR (95% CI)
All patients	39.38	73	1.9 (1.5, 2.3)
Gender			
Male	4.97	9	1.8 (0.8, 3.4)
Female	25.58	64	2.5 (1.9, 3.2)
Age groups, years			
<65 ($n = 252$)	18.18	48	2.6 (1.9, 3.5)
⩾65 ($n = 67$)	21.20	25	1.2 (0.8, 1.7)
SSc subsets			
lSSc	26.76	45	1.7 (1.2, 2.2)
dSSc	3.53	23	6.5 (4.1, 9.8)
SSc sine	7.91	5	0.6 (0.2, 1.5)

the elderly group, and both ILD and PAH were more frequent. Schachna *et al.* [20] also reported in a large scleroderma cohort that advanced age at disease onset was a risk factor for PAH. Oesophagic involvement was higher in younger SSc patients in our series, as it is known that oesophagic involvement is the most common systemic manifestation in SSc patients [9, 30], with chronic gastro-oesophageal reflux and motility dysfunction. No differences were found related to global gastrointestinal involvement between the two age groups. Regarding heart disease, in our patients, cardiac involvement was more frequent than has been reported in literature (54 *vs* 20–25%), and it was significatively higher in patients >65 years, mainly due to conduction system disease. Cardiac manifestations in SSc are diverse and usually indicate a poor prognosis. Heart disease can be secondary to other organ involvement (pulmonary or systemic hypertension) or can be due to primary myocardial disease, including myocarditis, heart failure, cardiac fibrosis, coronary artery disease, conduction system abnormalities and pericardial disease [9, 31]. Recently, Meune *et al.* [32] found a high prevalence of left ventricle (LV) and right ventricle (RV) systolic dysfunction and LV diastolic dysfunction independent of ILD and PAH, suggesting a primary myocardial involvement by SSc despite the absence of clinical manifestations. Renal disease was present in 6.6% of our patients, and only 4.4% had SRC. Sclerodermic renal disease and its more severe expression, SRC, have been frequently described in previous reports [19, 25]. The low incidence of renal crisis in our series could be due to the lesser frequency of the dSSc subset in the elderly patient group and to the extensive use of angiotensin-converting enzyme inhibitors. Sicca syndrome was also frequently reported in our SSc elderly patients, as has been reported in elderly patients with SLE [33]. We also found that in elderly SSc patients systemic manifestations appeared sooner than in young patients, particularly lung and heart involvement during the first 6 months after disease diagnosis. In addition, SSc was diagnosed frequently due to extracutaneous involvement in elderly patients. This could explain the shorter time between RP onset and SSc diagnosis in elderly patients despite the great proportion of lSSc patients.

Some of the differences in clinical manifestations of SSc in elderly patients could be explained by the physiological changes associated with the ageing process and the high incidence of some diseases in elderly patients, such as hypertension, heart failure, heart rhythm disturbances, and xerostomia and xerophtalmia [34].

Regarding immunological features, anti-topo I (anti-Scl70) was less frequently found in elderly patients than in younger patients, related to the greater number of lSSc patients in this group.

According to the literature, reports of survival rates in SSc differ considerably, mainly due to the initial time point from which survival has been estimated, taking into account the onset of SSc (Raynaud's beginning) or SSc diagnosis [11, 35, 36]. In agreement with other authors [35, 36], we determined survival from the time of disease diagnosis. In our series, 10-year survival was slightly higher than previously reported [11, 35] (global survival 81%, and 64% in patients aged ⩾65 years). This could be attributable to better management of SSc in internal organ involvement over recent years. It is difficult to interpret mortality rates without taking into account the expected mortality in the background population. The results of this work show a 1.9-fold increase in the mortality rate in SSc patients compared with an age- and sex-matched Spanish population, with a 2.6-fold increase in young and 1.2-fold increase in elderly patients. Thus, the mortality in the elderly was not significantly increased with respect to the background population. As expected, the mortality rate was significantly increased in the dSSc subset (SMR 6.5) and slightly increased in the lSSc subset (SMR 1.7) because of the more frequent internal organ involvement in the diffuse form.

Finally, 21 SSc patients aged >65 years died during follow-up and 19 of the 21 patients were directly related to SSc, mainly secondary to heart failure and PAH. Only one patient died due to a lung cancer, despite an increased incidence of lung cancer in patients with SSc being suggested [37, 38].

In summary, in elderly patients, the lSSc subset is more prevalent than the dSSc subset. Pulmonary and cardiac sclerodermic involvement are more prevalent in aged patients, and these systemic manifestations appear sooner after the disease diagnosis in this subgroup. It is important to point out that SSc diagnosis in advanced age is not infrequent, and that knowledge of the characteristics of this subgroup of patients and their differences compared with younger patients can help to improve the management of this disease, decreasing its morbidity and mortality.

Rheumatology key messages

- SSc diagnosis in advanced age is not infrequent.
- In elderly patients the lSSc subset is more prevalent than the dSSc subset.
- Pulmonary and cardiac involvement are more prevalent in aged patients.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Solans R, Motta C, Solà R *et al*. Abnormalities of erythrocyte membrane fluidity, lipid composition, and lipid peroxidation in systemic sclerosis. Arthritis Rheum 2000; 43:894–900.

2 Krieg T, Abraham D, Lafyatis R. Fibrosis in connective tissue disease: the role of the myofibroblast and fibroblast-epithelial cell interactions. Arthritis Res Ther 2007;9(Suppl. 2):S4.

3 Fonollosa V, Simeón CP. Esclerodermia. Med Clin 2004; 122:418–9.

4 Silman AJ. Epidemiology of scleroderma. Ann Rheum Dis 1991;50:846–53.

5 Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.

6 Le Roy EC, Black C, Fleischmajer R *et al*. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.

7 LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573–6.

8 Maricq HR, Spencer-Geen G, LeRoy EC. Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's síndrome and dermatomyositis. Am J Med 1976;61:862–70.

9 Black CM. Scleroderma: clinical aspects. J Intern Med 1993;234:115–8.

10 Poormoghim H, Lucas M, Fertig N, Medsger TA Jr. Systemic sclerosis sine scleroderma. Arthritis Rheum 2000;43:444–51.

11 Altman R, Medsger TA Jr, Bloch D, Michel B. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991;34:403–13.

12 Simeon CP, Armadans L, Fonollosa V *et al*. Mortality and prognostic factors in Spanish patients with systemic sclerosis. Rheumatology 2003;42:71–5.

13 Bryan C, Howard Y, Brennan P, Black C, Silman A. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. Br J Rheumatol 1996;35:1122–6.

14 Fried LP, Tangen CM, Walston J *et al*. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

15 Pu SJ, Luo SF, Wu YJ *et al*. The clinical features and prognosis of lupus with disease onset at age 65 and older. Lupus 2000;9:96–100.

16 Pease CT, Bhakta BB, Devlin J *et al*. Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors. Rheumatology 1999;38:228–34.

17 Marie I, Hatron PY, Levesque H *et al*. Influence of age on characteristics of polymyositis and dermatomyositis in adults. Medicine 1999;78:139–47.

18 Haga H, Johnsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. Scand J Rheumatol 1999;28:227–32.

19 Derk CT, Arlet CM, Jiménez SA. Morbidity and mortality of patients diagnosed with systemic sclerosis after the age of 75: a nested case-control study. Clin Rheumatol 2006;25:831–4.

20 Schachna L, Wigley FM, Chang B *et al*. Age and risk of pulmonary arterial hypertension in scleroderma. Chest 2003;124:2098–104.

21 Walker UA, Tyndall A, Czirják L *et al*. EUSTAR Co-authors. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma trials and research group database. Ann Rheum Dis 2007;66:754–63.

22 Berger M, Haimonitz A, Tosh AV, Berdoff R, Goldberg E. Quantitative assessment of pulmonary hypertensión in patients with tricuspid regurgitation using wave Doppler ultrasounds. J Am Coll Cardiol 1985;6:359.

23 Sánchez-Román J, Opitz CF, Kowal-Bielecka O, García-Hernández FJ, Castillo-Palma MJ, Pittrow D. for the EPOSS-OMERACT Group. Screening for PHA in patients with systemic sclerosis focus on Doppler-echocardiography. Rheumatology 2008;47:v33–5.

24 Castell J, Fraile M, Candell J *et al*. Myocardial perfusion imaging in scleroderma and Raynaud's phenomenon. Eur J Nucl Med 1992;19:660.

25 Traub YM, Shapiro AP, Rodnan GP *et al*. Hypertension and renal failure (scleroderma renal crisis) in progressive systemic sclerosis. Medicine 1985;62:335–52.

26 Taeger D, Sun Y, Keil U, Straif K. A stand-alone Windows application for computing exact person-years, standardized mortality ratios and confidence intervals in epidemiological studies. Epidemiology 2000;11:607–8.

27 Anonymous. Systemic sclerosis in old age. Br Med J 1979;1:1313–4.

28 Medsger TA Jr, Masi AT. Epidemiology of systemic sclerosis (scleroderma). Ann Intern Med 1971;74:714–21.

29 Laing TJ, Gillespie BW, Toth MB *et al*. Racial differences in scleroderma among women in Michigan. Arthritis Rheum 1997;40:734–42.

30 Marie I, Dominique S, Levesque H *et al*. Esophageal involvement and pulmonary manifestations in systemic sclerosis. Arthritis Rheum 2001;45:346–54.

31 Hunter C, Champion MD. The heart in scleroderma. Rheum Dis Clin N Am 2008;34:181–90.

32 Meune C, Avouac J, Wahbi K *et al*. Cardiac involvement is systemic sclerosis assessed by tissue-Doppler echocardiography during routine care. A controlled study of 100 consecutive patients. Arthritis Rheum 2008;58:1803–9.

33 Gilboe IM, Kvien TK, Uhlig T, Husby G. Sicca symptoms and secondary Sjögren's syndrome in systemic lupus erythematosus: comparison with rheumatoid arthritis and correlation with disease variables. Ann Rheum Dis 2001;60:1103–9.

34 Walston J, Hadley EC, Ferrucci L *et al*. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on aging research conference on frailty in older adults. J Am Geriatr Soc 2006;54:991–1001.

35 Ferri C, Valentini G, Cozzi F. for the Systemic Sclerosis Study Group of the Italian Society of Rheumatology. Systemic sclerosis. Demographic, clinical and serologic features in 1012 Italian patients. Medicine 2002;81:139–53.

36 Scussel-Lonzetti L, Joyal F, Raynaud JP *et al*. Predicting mortality in systemic sclerosis. Analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine 2002;81:154–67.

37 Abu-Shakra M, Gulemin F, Lee P. Cancer in systemic sclerosis. Arthritis Rheum 1993;36:460–4.

38 Pontifex EK, Hill CL, Roberts-Thomson P. Risk factors for lung cancer in patients with scleroderma: a nested case-control study. Ann Rheum Dis 2007;66:551–3.