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Systemic sclerosis mortality in the United States: 1979–1998

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Abstract. The US national mortality rates from systemic sclerosis (SSc) have not been reported since 1979. We studied age, gender and race specific time trends in US national mortality rates of SSc during the period 1979–1998 using poisson regression models. Over the 4.93 billion person-years of observation during the study period, there were 18,126 deaths from SSc, representing a mortality rate of 3.9 per million. The age adjusted mortality rates for men and women were 1.9 and 5.4 per million respectively. There were relatively few deaths in the extremes of age. SSc mortality rates increased with age in both genders and in all racial groups ($p < 0.001$). In multivariable models adjusted for two-way statistical interactions, being African–American, female and of older age were associated with higher death rates. Over the 20 years of observation, overall (age-adjusted) SSc mortality rates showed a 36% increase ($p < 0.001$) and subgroup analyses revealed that the increases were confined to women of both races. This rise occurred during a period in which post-diagnosis survival of SSc is known to have increased, suggesting an increasing incidence of this disease.

Key words: Epidemiology, Complications, Mortality, Systemic sclerosis, Trends

Abbreviations: SSc = systemic sclerosis; SMR = standardized mortality ratio; US = United States

Introduction

Systemic sclerosis (SSc) is a clinically heterogeneous and generalized disorder which affects the connective tissue of the skin and internal organs such as gastrointestinal tract, lungs, heart and kidneys. It is characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen resulting in cardiac, pulmonary and renal failure [1–4]. The diagnosis of this condition is primarily clinical with laboratory testing providing additional support. The hallmark of the clinical diagnosis of SSc is the thickening and hardening of the skin (scleroderma) associated with abnormal capillary sensitivity to cold leading to bluish and whitish discoloration of extremities (Raynaud's phenomenon).

The underlying pathological process is fibrosis of the tissue with concomitant reduction in blood circulation in small blood vessels such as capillaries. Internal organs such as heart lungs kidneys and blood vessels are sometimes involved leading to organ failure and death. Laboratory tests reveal presence of antibodies to cell nuclear antigens (Anti-nuclear antibodies – ANA). The term "antinuclear antibodies" describes a variety of autoantibodies that react with constituents of cell nuclei, including DNA, RNA, and several proteins and ribonucleoproteins. The Scl-70 antibody is an antibody to extractable nuclear antigens and a commonly ordered tests for those who are suspected or clinically diagnosed to have SSc. Scl-70 antibodies are considered highly specific but are not very sensitive for SSc. There is considerable variation in assay sensitivity for this antibody, especially in the last decade. It is also likely that these tests have been more standardized in recent years and therefore more reliable. There is little data available on temporal trend in testing for Scl-70 and other autoantibodies; However, these laboratory tests do not establish the diagnosis and clinical evaluation is the gold standard [5].

The etiology of SSc is not known. Known risk factors include environmental and occupational exposures to vinyl chloride, adulterated cooking oils, L-tryptophan, silica, silicone breast implants, organic solvents, and other agents such as epoxy resins, pesticides, and hand/arm vibration [6]. Familial clustering has been noted. Women are at higher risk of developing this disease and African-Americans are more likely than Caucasians to be diagnosed with this condition [7]. African-Americans have a lower age at onset, as well as a higher frequency of diffuse skin involvement, pulmonary disease, and an overall worse prognosis than Caucasians [8].

SSc has an incidence of 20 per million per year [3]. The risk of death from this condition is directly proportional to the extent of anatomical involvement of skin and viscera. Patients with SSc are much more

likely to die than the age-gender matched general population with a standardized mortality ratio (SMR) of 2–4 [9, 10]. In a retrospective 'inception cohort' based single rheumatology practice, the case-fatality ratio was reported to be between 2% and 4% per year [11].

In the US, national mortality rates from SSc have been described in the years prior to 1978[7, 12–14]. In the period from 1959 to 1961, death rates in the US from SSC were estimated to be 2.1 per million for women and 1.0 million for men [14]. The latest study that spanned the years 1969 through 1977 showed death rates of 3.5 per million and 1.4 per million for women and men respectively [15]. There have been no studies on national mortality rates since. We describe here, data on national SSc mortality rates during the period from1979 to1998.

Methods

Data from the county level national mortality and population data, (derived from records of all deaths that occurred in the United States) during the period from 1979 to 1998 were obtained from the National Center for Health Statistics (URL: http://www.cdc.gov.nchs/). ICD-9 code 710.1 was used to identify SSc-caused deaths.

Annual cause-specific mortality rates (expressed as per million population)were calculated by dividing the number of deaths from SSc in a year by the corresponding U.S. residential population estimates obtained from the U.S. Bureau of the Census. Age-adjusted rates were calculated by applying the age-specific rates to a single standard US population for the year 2000 [16]. All rates presented here are age-adjusted unless otherwise specified. When overall rates were calculated for the entire period, pooling data across years, rates were expressed as number of SSc deaths per million person-years.

Racial data collected during a major part of the study period included only four categories: African-American, Caucasian, Native American and Asian or Pacific Islander. The number of deaths in these last two categories were too small (n = 771 in 181 million person years) for meaningful analyses and therefore were not presented in this report. When the number of deaths fall below 20, the relative standard error of the rate estimate becomes greater than 23% and this estimate is considered unreliable. Therefore, when providing age-sex specific rates, we have utilized all age groups. However, for modeling time trends, we used only deaths above the age 20 because of potential biases by small numbers.

For studying the relative importance of age, gender, and race we fitted multivariable Poisson regression models where the number of deaths was the dependent variable of interest. The person years of observation for each stratum of the above variables were accounted for in all the models. This regression estimates the relative risk (RR) of death in each variable stratum in the model and their 95% confidence interval (95% CI), as well as p -values for statistical significance. Poisson regression was also used for testing time trends for statistical significance. We hypothesized that there was an underlying biological effect modification between age, race and gender, two-way interaction terms (age–gender, gender–race and age–race) were tested for statistical significance along with the respective main effects. These were included in the model to derive adjusted relative risk of each of the covariates. The fit of each of the models was assessed by computing log-likelihood. The larger the magnitude of this metric, the better fitting the model is. The fit of the model with interaction terms was statistically compared by likelihood ratio test to that of a model that did not include the interaction terms. All analyses were performed using STATA® (College Station, TX). Institutional Review board approval was not sought as this study used publicly available data in aggregate form that precludes identification of individual subjects.

Results

Over the 4.93 billion person-years of observation during the period from 1979 to 1998, 22.3 million men and 20.6 million women in the US died of all causes. Of this 18,126 deaths were reported to be due to SSc. This represented an overall age adjusted SSc mortality rate of 3.9 per million person-years. The SSc death rates for women and men were 5.4 per million and 1.9 per million ($p < 0.001$). This excess risk was observed in both African-Americans and Caucasians, with the former having a higher death rate (6.5 per million versus 3.6 per million, $p < 0.001$) [Age adjusted relative risk 2.9, 95% confidence interval 2.8–3.0)].

The overall age and gender specific mortality rates are presented in Table 1. There were few deaths from SSc among people less than 25 years of age over the 20 years of observation (death rate 0.11 per million). Similar to other diseases and to the overall population death rates, SSc mortality rates increased with age (RR 1.30 per age stratum, 95% CI 1.28–1.31). Detailed age-gender and race specific death rates are shown in Tables 2 and 3. Mortality rates increased with age with a peak rate of 7.5 per million (age group 74–84) for Caucasian men and 12.2 per million for African–American men. Mortality rates also increased with age among women with a peak death rate of 22.4 per million (age group 65–74) for African–American women and 21.6 per million (age group 75–84) for Caucasian women. Among the oldest age group (85 years or more) the rates were 11.8 per million for women (505 deaths) and 4.1 per million (70 deaths) for men. All these

Table 1. Overall age–gender specific mortality rates (per million) from systemic sclerosis in the United States, 1979–1998

Age–group (years)	Women			Men		
	N	Person-years	Death rate	N	Person-years	Death rate
< 1	1	37,518,157	0.0*	1	39,383,988	0.0*
1–4	0	143,382,548	0.0*	2	150,200,410	0.0*
5–9	6	174,483,890	0.0*	3	182,928,692	0.0*
10–14	23	175,934,992	0.1	3	184,545,329	0.0*
15–19	27	184,889,189	0.1	10	193,605,259	0.1*
20–24	93	196,383,192	0.5	30	201,110,744	0.1
25–34	474	413,334,504	1.1	126	412,884,311	0.3
35–44	1107	359,325,487	3.1	351	350,858,653	1
45–54	1962	268,223,807	7.3	686	255,191,453	2.7
55–64	3209	228,850,487	14	1082	204,485,360	5.3
65–74	4180	196,381,974	21.3	1114	153,781,918	7.2
75–84	2512	121,227,999	20.7	549	73,432,145	7.5
> 85	505	43,209,690	11.7	70	17,134,406	4.1

*Unreliable rates.

age-related trends were statistically significant ($p < 0.001$).

The individual effects of age, gender and race on the risk of death were studied in univariable Poisson regression models, where the number of deaths was the dependent variable and the characteristic of interest was the independent variable. All three were highly significant. Univariable relative risk for age was 1.59 (95% CI 1.58, 1.61), female gender 3.14 (95% CI 3.02, 3.25) and for African-American race 1.61 (95% CI 1.55, 1.67). These were entered into the multivariable model where all remained statistically significant (Table 4, Model 1). Two-way tests for interaction between age, gender and race variables were highly significant ($p < 0.001$) and they were added to the above model to derive the final model (Table 4, Model 2). This provided a better reflection of the data (Likelihood test $p < 0.0001$). In this model, African – American race was the most powerful determinant of mortality risk followed by female gender and increasing age, respectively.

The time trends in mortality are plotted in Figure 1. Data used for the table is given in able format in the appendix. Overall the mortality increased by ~36% ($p < 0.001$). For Caucasian men the rate remained stable at ~1.8 per million while for Caucasian women, the rate increased from 3.9 in 1979 to 6.6 in 1998, representing ~70% increase ($p < 0.001$). For African – American men the rate decreased from 4.7 to 3.6 ($p = 0.04$). Among African – American Women the rate showed a slow but increasing trend ($p = 0.014$).

Discussion

This is the first study that presents the US national mortality rates of SSc in recent years. The primary observation we have documented is the higher

Table 2. Age–gender specific mortality rates (per million) from systemic sclerosis among Caucasians: United States, 1979–1998

Age–group (years)	Women			Men		
	N	Person-years	Death rate	N	Person-years	Death rate
< 1	1	29,908,146	0.0*	1	31,499,860	0.0*
1–4	0	114,441,964	0.0*	2	120,513,509	0.0*
5–9	5	139,554,938	0.0*	0	147,068,512	0.0*
10–14	15	141,387,170	0.1*	1	149,102,562	0.0*
15–19	15	149,455,724	0.1*	4	157,350,195	0.0*
20–24	35	160,295,959	0.2	12	166,266,482	0.1*
25–34	241	340,638,576	0.7	71	347,376,078	0.2
35–44	656	300,781,124	2.2	217	299,839,777	0.7
45–54	1423	228,985,726	6.2	488	221,873,923	2.2
55–64	2633	199,796,890	13.2	845	181,183,803	4.7
65–74	3735	174,990,432	21.3	971	138,295,026	7
75–84	2364	110,112,351	21.5	497	66,647,446	7.5
> 85	478	39,615,598	12.1	60	15,494,862	3.9

*Unreliable rates.

Table 3. Age – gender specific mortality rates (per million) from systemic sclerosis among African – Americans: United States, 1979–1998

Age – group (years)	Women			Men		
	N	Person-years	Death rate	N	Person-years	Death rate
< 1	0	6,024,199	0.0*	0	6,206,953	0.0*
1–4	0	22,690,531	0.0*	0	23,213,081	0.0*
5–9	1	27,569,778	0.0*	3	28,220,769	0.1*
10–14	8	27,200,249	0.3*	2	27,796,276	0.1*
15–19	12	28,181,188	0.4*	5	28,545,008	0.2*
20–24	54	28,181,242	1.9	17	26,589,722	0.6*
25–34	215	54,941,895	3.9	53	48,800,091	1.1
35–44	412	43,652,179	9.4	126	37,472,213	3.4
45–54	471	29,761,652	15.8	184	24,752,290	7.4
55–64	508	22,855,496	22.2	221	18,067,594	12.2
65–74	390	17,390,042	22.4	133	12,268,431	10.8
75–84	125	9,398,417	13.3	46	5,416,164	8.5
> 85	24	3,130,614	7.7	9	1,336,560	6.7*

*Unreliable rates.

mortality rate among women compared to men (3.5 times greater). This differential risk persisted even after adjusting for age, race and their two-way interactions. In contrast, in the general US population, men had a 1.6 times higher age adjusted mortality rate than women. This reversal of mortality risk in SSc is consistent with the incidence and prevalence studies that show a 3–5 times higher frequency among women [7, 17, 18]. Similarly, women with SSc have a five fold higher hospital admission rate compared to men [19]. Gender-specific hormonal and biological factors, as well as environmental factors have been cited as putative causes of this gender differential [3, 7, 20]. Another potential reason may be that men, having higher overall mortality rates, are likely to die of other causes such as cancer and coronary artery disease before SSc can advance to end organ damage and death. Thus in a Danish study of 344 cases of SSc only 26% of deaths were directly related to SSc [9]. In the British study that used an 'inception cohort', 52% of deaths among men were unrelated to Ssc while the corresponding figure among women was only 34% [11]. This may also explain the observation from some survival studies that men, not women, have an adverse prognosis [20–22].

African – Americans are known to have higher incidence, prevalence and mortality rates from SSc [7, 20]. Since African-American women are known to have a higher prevalence of SCL-70 antibodies than Caucasian women [7, 20], and also have a greater predisposition to have diffuse SSc, these factors may account for the higher mortality risk we see in our analyses. Interestingly the age–gender, gender–race and age–race interaction variable in the poisson models were significant. This indicates, as we had hypothesized, the effect of each of race, age and

Table 4. Poisson regression models for predictors of mortality of 18,126 systemic sclerosis deaths observed over 4.93 billion person years during the period 1979–1998

Factors*	Relative risk	95% Confidence interval	*p* value	Model pseudo R^2
				0.79
Model 1 (Unadjusted for interaction)				
Ten year increase in age	1.56	1.69–1.76	< 0.001	
Male	1.00			
Female	2.69	2.59–2.78	< 0.001	
Caucasian	1.00			
African – American	1.85	1.78–1.93	< 0.001	
				0.82
Model 2 (Adjusted for interaction)				
Ten year increase in age	1.73	1.69–1.76	< 0.001	
Male	1.00			
Female	3.92	3.55–4.33	< 0.001	
Caucasian	1.00			
African – American	5.40	4.81–6.05	< 0.001	

The following two-way interactions were adjusted for: age–gender, age–race and race–gender.

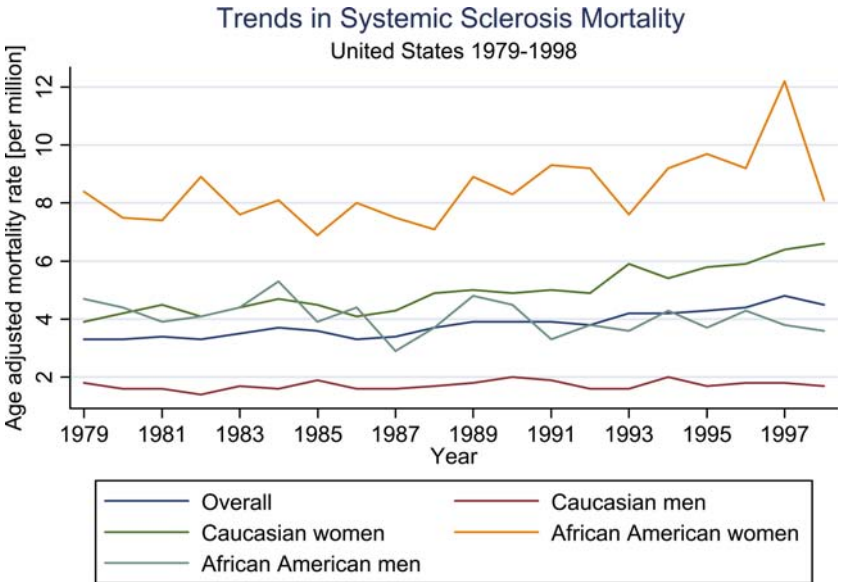

Figure 1. Time trends in systemic sclerosis mortality in the US, 1979–1998.

gender were conditional upon the status of the others, suggesting an underlying biological effect modification.

While the association between mortality and advancing age is well documented [3, 11], the age-specific pattern in our study showed interesting racial differences. Death rates peaked about 10 years earlier among African–Americans compared to Caucasians. This observation parallels population based observations in the US which show that the mean age of onset of SSc among African-Americans is 10 years earlier than among Caucasians (44 vs. 56 years) [7].

Another interesting observation we made is the rise in US national SSc mortality rates from 1978–1998. This is consistent with the observed increases in incidence and stable prevalence of this disease. For example during the period from 1973 to 1982, the incidence of SSc in a geographically circumscribed cohort doubled by comparison to the previous 10 year period. There are other possible explanations. The diagnostic practices may have changed substantially leading to a greater apparent incidence of the disease. While this is plausible, there have been no substantial changes in the diagnostic criteria for SSc over the time period studied. The use of antibody testing may have increased substantially even though many of these tests, including Scl-70 are of variable assay sensitivities. In fact these tests are not as sensitive as they are specific, making this a less likely confounder for the observed trends. Attribution bias in the manner in which death certificates are completed may be another explanation for our observation. However, methodological research suggests that while death certificate data tend to underestimate SSc mortality the bias is likely to be constant over time [23].

Similar to national mortality statistics from cancer and cardiovascular diseases, the SSc mortality rates we have presented is based on death certificate data. These data are not without shortcomings. Since most of the death certificates in the US are completed by primary care physicians, rather than rheumatologists, nephrologists or pulmonologists, SSc may not be mentioned at all as contributing or proximate causes of death. Even in case series' from speciality centers, a large proportion (30–50%) of patients died of causes such as infection, cancer and coronary artery disease [9, 11]. Thus the mortality rates we have reported are likely to be an underestimate of the true population mortality. Lastly, since the survival from SSc has improved substantially over time, these survivors are increasingly likely to die from competing causes of death such as stroke, heart attack etc. Such a phenomenon would lead to fewer deaths attributed to SSc and therefore tend to bias the observed time trend downward.

Conclusions

Deaths from SSc are rare in extremes of age. Women, especially African – American women, have the highest death rates from SSc. The overall SSc mortality rates showed a 36% increase during the period from 1979 to 1998. This rise was marked in Caucasian women and occurred during a period in which post-diagnosis survival of SSc is known to have increased, suggesting an increasing incidence of this disease.

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Appendix

1980 criteria for the classification of systemic sclerosis [1]

Major criterion:
Proximal diffuse (truncal) sclerosis (skin tightness, thickening, non-pitting induration)
Minor criteria:
Sclerodactyly (only fingers and/or toes)
Digital pitting scars or loss of substance of the digital finger pads (pulp loss)
Bibasilar pulmonary fibrosis

The patient should fulfill the major criterion or two of the three minor criteria.

Age adjusted SSc mortality rates in the United States: 1979–1998

Year	Caucasian men	Caucasian women	African–American women	African–American men	Overall
1979	1.8	3.9	8.4	4.7	3.3
1980	1.6	4.2	7.5	4.4	3.3
1981	1.6	4.5	7.4	3.9	3.4
1982	1.4	4.1	8.9	4.1	3.3
1983	1.7	4.4	7.6	4.4	3.5
1984	1.6	4.7	8.1	5.3	3.7
1985	1.9	4.5	6.9	3.9	3.6
1986	1.6	4.1	8	4.4	3.3
1987	1.6	4.3	7.5	2.9	3.4
1988	1.7	4.9	7.1	3.7	3.7
1989	1.8	5	8.9	4.8	3.9
1990	2	4.9	8.3	4.5	3.9
1991	1.9	5	9.3	3.3	3.9
1992	1.6	4.9	9.2	3.8	3.8
1993	1.6	5.9	7.6	3.6	4.2
1994	2	5.4	9.2	4.3	4.2
1995	1.7	5.8	9.7	3.7	4.3
1996	1.8	5.9	9.2	4.3	4.4
1997	1.8	6.4	12.2	3.8	4.8
1998	1.7	6.6	8.1	3.6	4.5

References

1. Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma). Ann Intern Med 1962; 57: 305–319.
2. Steen VD, Medsger TA Jr. Epidemiology and natural history of systemic sclerosis. Rheum Dis Clin North Am 1990; 16(1): 1–10.
3. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin North Am 2003; 29(2): 239–254.
4. Medsger TA, Jr., Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W.. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003; 21(3 Suppl 29): S42–46.
5. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980; 23(5): 581–590.
6. Nietert PJ, Silver RM. Systemic sclerosis: environmental and occupational risk factors. Curr Opin Rheumatol 2000; 12(6): 520–526.
7. Mayes MD, Lacey JV Jr., Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003; 48(8): 2246–2255.
8. Reveille JD. Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics, and clinical manifestations. Curr Rheumatol Rep 2003; 5(2): 160–167.
9. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998; 37(7): 750–755.
10. Simeon CP, Armadans L, Fonollosa V, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. Rheumatology (Oxford) 2003; 42(1): 71–75.
11. 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(11): 1122–1126.
12. Medsger TA, Jr., Masi AT. Epidemiology of systemic sclerosis (scleroderma). Ann Intern Med 1971; 74(5): 714–721.
13. Medsger TA, Jr., Masi AT. The epidemiology of systemic sclerosis (scleroderma) among male U.S. veterans. J Chronic Dis 1978; 31(2): 73–85.
14. Cobb S. The Frequency of Rheumatic Diseases (Vital & Health Statistics Monographs, American Public Health Association). Cambridge: Harvard University Press, 1971.
15. Hochberg MC, Lopez-Acuna D, AM G. Mortality from systemic sclerosis (scleroderma) in the United States 1969–1985, Systemic Sclerosis (scleroderma). In: Black CM and AR M (eds): Systemic Sclerosis (scleroderma). New York: Gower, 1985, p. 61–69.
16. Hoyert DL, Anderson RN. Age-adjusted death rates: trend data based on the year 2000 standard population. Natl Vital Stat Rep 2001; 49(9): 1–6.
17. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA, Jr. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963–1982. Arthritis Rheum 1997; 40(3): 441–445.
18. Chandran G, Smith M, Ahern MJ, Roberts-Thomson PJ. A study of scleroderma in South Australia: prevalence, subset characteristics and nailfold capillaroscopy. Aust N Z J Med 1995; 25(6): 688–694.
19. Nietert PJ, Silverstein MD, Silver RM. Hospital admissions, length of stay, charges, and in-hospital death among patients with systemic sclerosis. J Rheumatol 2001; 28(9): 2031–2037.
20. Laing TJ, Gillespie BW, Toth MB, et al. Racial differences in scleroderma among women in Michigan. Arthritis Rheum 1997; 40(4): 734–742.

21. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore) 2002; 81(2): 139–153.
22. Silman AJ. Epidemiology of scleroderma. Ann Rheum Dis 1991; 50(4): 846–853.
23. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Systemic sclerosis prevalence and mortality in Sydney 1974–1988. Aust N Z J Med 1999; 29(1): 42–50.

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