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Systemic Sclerosis

Demographic, Clinical, and Serologic Features and Survival in 1,012 Italian Patients

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease clinically characterized by different degrees of skin fibrosis and visceral organ involvement (17, 19, 22). The etiology of SSc remains obscure; the disease appears to be the result of a multistep and multifactorial process, including immune system alterations, genetic and exogenous, and toxic or infectious factors (17, 19, 22). The epidemiology of SSc is not definitely established due to the relative rarity of the disease, the difficulty in diagnosis, and its extreme clinical variability. SSc affects females more frequently than males, with a peak of incidence between ages 45 and 64 years (19, 22). There seems to be an increased incidence of the disease in blacks, particularly in black females, but no other significant racial differences in distribution. Various HLA studies in SSc patients failed to identify any clearcut associations, even if a role of specific HLA antigens might be hypothesized for particular clinico-serologic SSc subsets (19). Moreover, familial factors are certainly important for SSc development: it is not rare to observe a scleroderma patient with 1 or more first-degree relatives with another autoimmune systemic disorder, such as Raynaud phenomenon, systemic lupus, or rheumatoid arthritis (19, 22).

The annual incidence (new cases/population at risk per year) of SSc varies largely among different surveys (from 0.6 to 19.1 per million/year), as does the estimated prevalence (number of cases living at a particular time or during a given time interval per million of population at risk: from 126 to 1,500). The actual incidence and prevalence of the disease are generally underestimated; the minimum estimated values are 20/million per year and 1,500/million, respectively. The number of undiagnosed cases, especially in the oldest surveys, might be significant; this is due, at least in part, to the clinical characteristics of the disease. SSc includes a wide spectrum of symptoms, varying from very mild cutaneous and internal organ involvement to diffuse fibrosis responsible for organ failure (4, 11, 17, 19, 22).

A variable combination of organ damage, or, less frequently, a severe, single organ involvement, is responsible for SSc morbidity and mortality. Among different connective tissue diseases, SSc shows the poorest prognosis (17, 19, 22). The availability of well-recognized criteria for diagnosis, disease activity (34), and severity (21), as well as of valuable prognostic parameters, should be decisive for timely patient identification, clinical assessment, and management. In the absence of valuable diagnostic criteria, patients are usually classified according to the American College of Rheumatology (formerly ARA) preliminary criteria for SSc classification (32) (Table 1). The introduction of capillaroscopic SSc pattern (capillary dilation with or without capillary dropouts) and SSc-related serum autoantibodies might improve the usefulness of classification criteria, particularly in discriminating the early stage of the dis-

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TABLE 1. Classification criteria and diagnostic parameters of systemic sclerosis (SSc)

Preliminary Classification Criteria*	Main Diagnostic Parameters
Major criterion	Proximal skin sclerosis
Proximal scleroderma	Sclerodactyly
Minor criteria	Raynaud phenomenon
Sclerodactyly	Digital pitting scars
Digital pitting scars	Bibasilar pulmonary fibrosis
Bibasilar pulmonary fibrosis	Esophageal dysfunction
	Telangiectasias
	Calcinosis
	Capillaroscopic SSc pattern
	Serum autoantibodies†

*American College of Rheumatology (formerly ARA) 1980 Criteria (ref. 32): the major criterion or any combination of 2 or more minor criteria was found in 97% of definite SSc patients (sensitivity) and in 2% of comparison cases (98% specificity). Localized scleroderma and pseudoscleroderma disorders represent criteria of exclusion.

†Anti-Scl70, anti-centromere, anti-nucleolar antibodies.

TABLE 2. Approach to apparently isolated Raynaud phenomenon

1. Exclusion of other conditions
2. Accurate history and complete physical examination to identify any sign or symptom of connective tissue disease (arthritis, dysphagia, telangiectasias, digital ulcers, or pitting scars, calcinosis)
3. Nailfold capillaroscopy
4. Autoantibody detection

Raynaud phenomenon (RP) classification

Type I:	Primary, isolated RP
Type II:	Suspected secondary RP. Presence of 1 or more clinical, serologic, or capillaroscopic alterations not sufficient for diagnosis of definite disease
Type III:	Secondary RP

ease. However, these criteria are not intended to assist in the diagnosis of individual patients, which is based on the careful observation of different clinical and laboratory features.

Diagnosis of SSc in patients with diffuse cutaneous sclerosis is quite easy; on the contrary, it can be particularly difficult during the early stage of the disease or in the presence of sine scleroderma SSc (ssSSc) (Figure 1). In these instances, isolated Raynaud phenomenon (Table 2) or other connective tissue diseases must be ruled out. Diagnosis of SSc is currently based on the presence of cutaneous manifestations (symmetrical, truncal, and/or acral skin sclerosis, skin ulcers, digital pitting scars, telangiectasias, calcinosis), typical internal organ involvement (lung fibrosis, esophageal dysfunction, heart and/or renal alterations), capillaroscopic scleroderma pattern, and autoantibody profile (see Table 1, Figures 1–3).

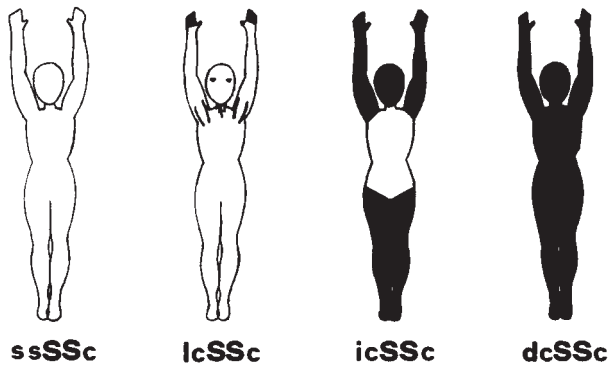

FIG. 1. Systemic sclerosis (SSc) classification according to skin sclerosis extent (black areas). Sine scleroderma SSc (ssSSc): absence of cutaneous sclerosis in patients with typical SSc visceral organ involvement, capillaroscopic changes, and serum autoantibodies. Limited cutaneous scleroderma (lcSSc): skin sclerosis of fingers (sclerodactyly) with or without mild sclerotic lesions at neck, face, and armpits. Intermediate cutaneous scleroderma (icSSc): sclerosis of upper and lower limbs, neck and face, without truncal involvement. Diffuse cutaneous scleroderma (dcSSc): distal and truncal skin sclerosis.

The large variability in the disease course, generally characterized by progressive, often subclinical, visceral organ deterioration, makes the long-term outcome of SSc extremely unpredictable. The clinical and autoantibody pattern of the disease observed in different patient populations may also vary widely (2, 8, 10–15, 17, 19, 22, 30, 31, 35). The relationship between clinico-serologic features of SSc and survival rates can give us useful prognostic parameters. Moreover, follow-up studies on different patient series can yield new insights on the possible variations of SSc pathomorphism during the last few decades. These changes could be the consequence of different racial and etiopathogenetic factors, as well as of improved therapeutic strategies. In this light, we retrospectively investigated demographic and clinico-serologic features in a large cohort of Italian patients with SSc, and their relationship to survival.

Patients and Methods

In 1997 the Italian Society of Rheumatology (SIR) promoted the present study involving 3 University-based divisions of rheumatology from the north (University of Padova), center (University of Pisa), and south (University of Napoli) of Italy with comparable, long-term experience in SSc patient management.

Patients

The study population was recruited between 1955 and 1999 at the 3 participating centers. One thousand twelve patients (897 fe-

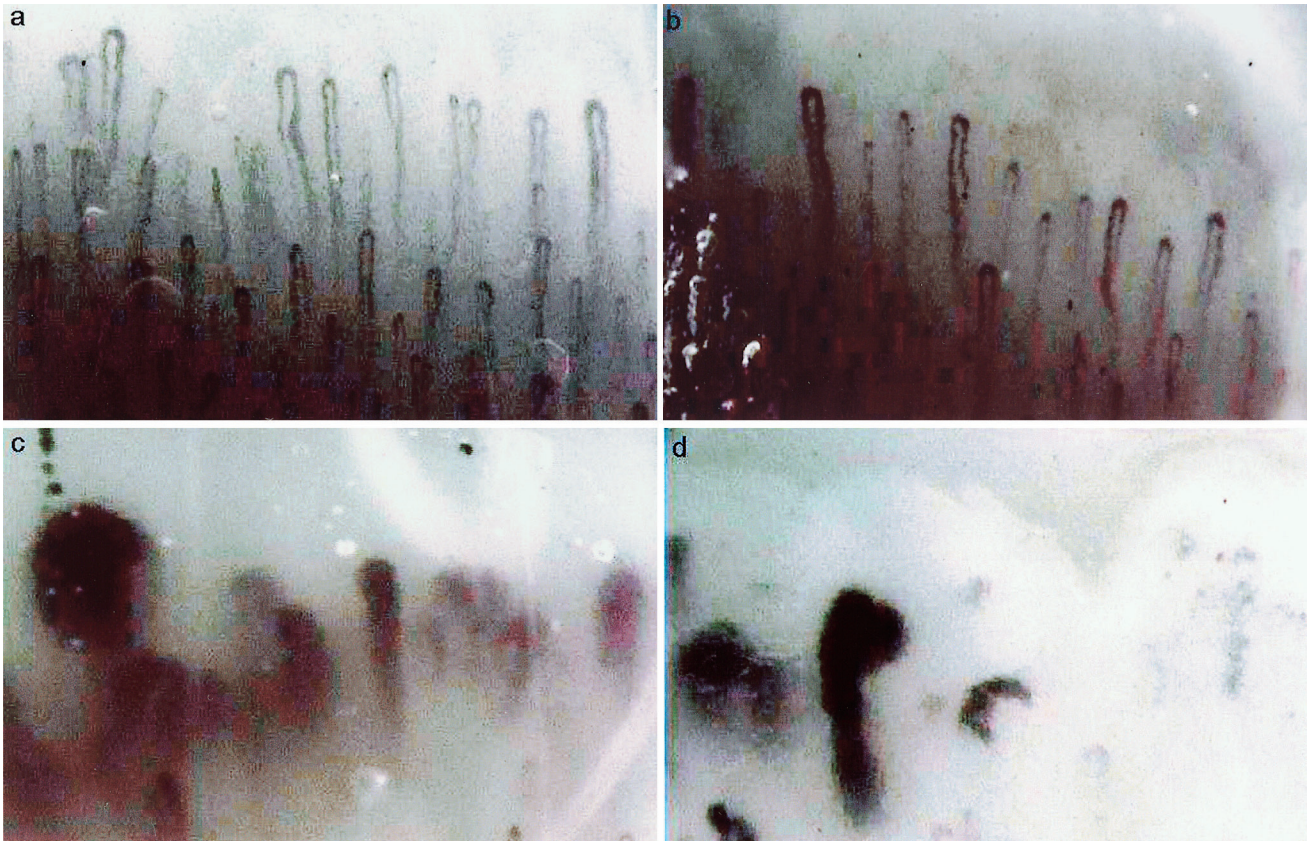

FIG. 2. Capillaroscopic findings. **a.** Normal subject. **b.** Patient with isolated Raynaud phenomenon. **c.** and **d.** Typical scleroderma patterns: **c.** diffuse capillary enlargement (megacapillaries), **d.** presence of megacapillaries and large avascular areas (capillary dropouts).

males, 115 males; mean age at presentation, 50.5 ± 13.8 SD years; see Table 3) were included in the study; namely, 323 patients from Padova were collected between 1978 and 1999, 349 from Pisa between 1972 and 1999, and 340 from Napoli between 1955 and 1999.

At the beginning of the follow-up, corresponding to the time of diagnosis, all patients fulfilled the American College of Rheumatology (formerly ARA) criteria for SSc classification (32; see Table 1). At the same time, patients were also classified based on the extent of skin sclerosis according to the 3-cutaneous subset model (18). These subsets are 1) limited cutaneous scleroderma (lcSSc): sclerosis of fingers with or without sclerosis of the neck and/or face; 2) intermediate cutaneous scleroderma (icSSc): sclerosis of upper and lower limbs, neck, and face, without truncal involvement; and 3) diffuse cutaneous scleroderma (dcSSc): distal and truncal skin sclerosis (see Figure 1). For the survival study patients were also grouped according to the 2-cutaneous subset classification (17, 19, 22, 31); namely, patients were classified as having limited cutaneous scleroderma (sclerosis of distal extremities, not above the elbow and knees, with or without sclerosis of neck and face) or diffuse cutaneous scleroderma (sclerosis of both distal and proximal extremities, with or without truncal involvement). Patients with ssSSc were invariably included in the lcSSc subset (12, 26).

Clinical assessment

Epidemiologic and clinico-serologic assessment was carried out at different centers using data from patient records in 3 main categories: demographic data and symptoms at SSc onset, clinical features observed at the time of referral, and cumulative clinical manifestations observed during the entire follow-up.

Standardized criteria were followed for the evaluation of clinical symptoms (11, 12). In particular, the age at disease onset was considered to be the age at which the first signs and symptoms compatible with the disease appeared; namely, Raynaud with digital ischemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnea, and/or dysphagia.

Organ involvement was evaluated according to the criteria previously described (11, 12) with some modifications. In particular, each type of involvement was defined as follows: 1) peripheral vascular: Raynaud phenomenon with digital pitting scars (see Figure 3) and/or ulcerations or gangrene; 2) joint: presence of polyarthralgia or arthritis when inflammatory changes were observed in more than 2 joints; 3) muscle: isolated muscle weakness or weakness associated with elevated serum creatine kinase with or without electromyographic or histologic changes of inflammatory myopathy; 4) esophageal: dysphagia and or esophageal radio-

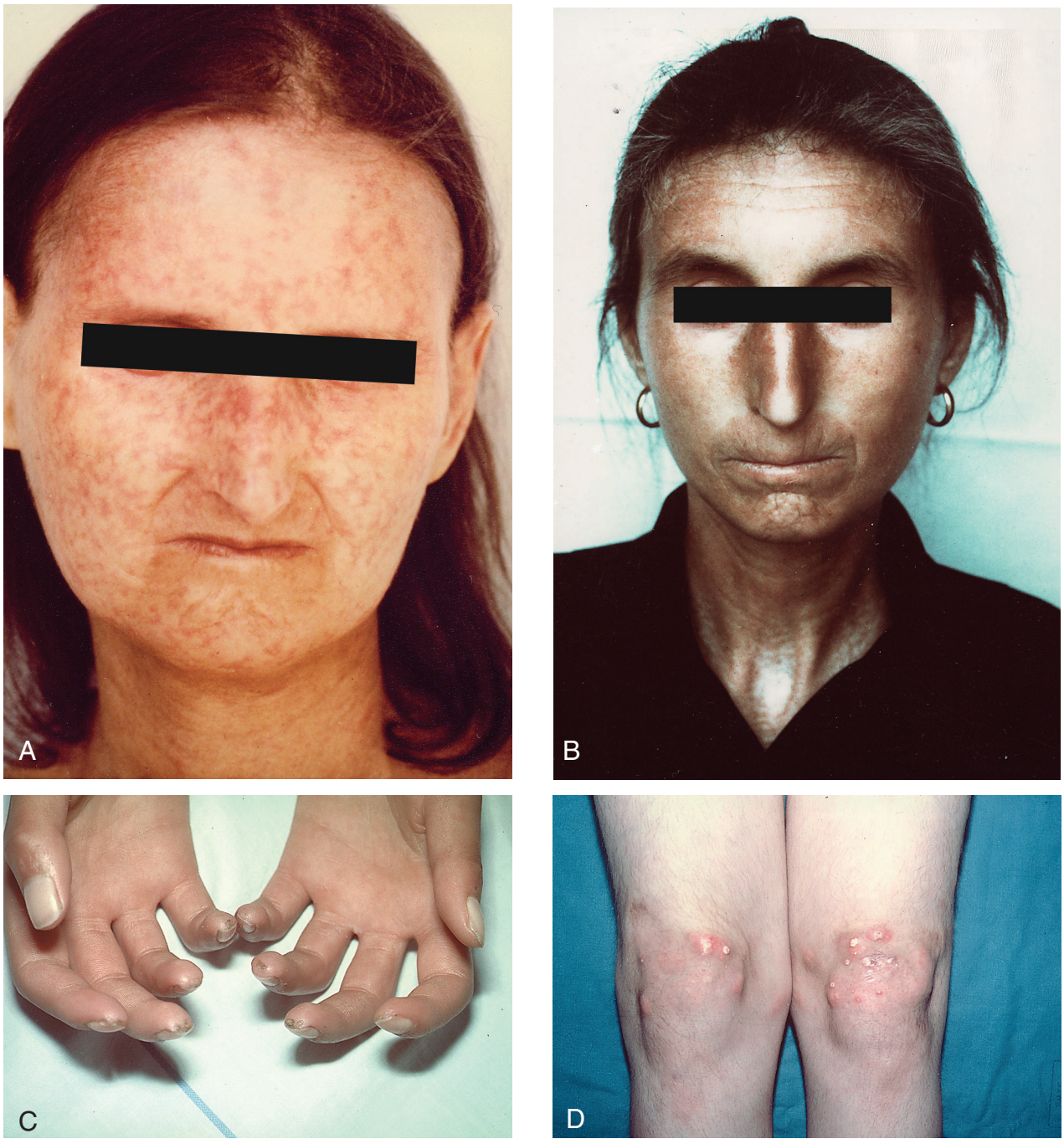

FIG. 3. Cutaneous manifestations of SSc. **A.** Patient with limited cutaneous SSc (lcSSc): mild perioral sclerosis and diffuse telangiectasias. **B.** Patient with diffuse cutaneous SSc: marked skin sclerosis at face and neck, diffuse hypermelanosis with some hypochromic areas. **C.** Digital pitting scars and pulp ulcers in lcSSc. **D.** Subcutaneous calcinosis at knees in lcSSc.

graphic dysmotility; 5) pulmonary: bibasilar fibrosis at standard chest X-ray and/or restrictive lung disease on pulmonary function tests and/or pulmonary hypertension; 6) cardiac: at least 1 of the following symptoms: pericarditis, congestive heart failure, severe arrhythmias, and/or atrioventricular conduction abnormalities; 7) renal: scleroderma renal crisis with increased diastolic blood pressure and/or progressive renal failure.

Laboratory findings

At the beginning and/or during the follow-up, the presence of serum autoantibodies was investigated in 755 SSc patients by means of standard techniques (11, 12): antinuclear (ANA) and antinucleolar antibodies (ANoA) by indirect immunofluorescence on rat liver (dilution 1:20) and/or on Hep-2 cell lines (dilution 1:40); anticentromere antibodies (ACA); antiextractable nuclear antigen (ENA) antibodies, including anti-Scl70, -Sm, -RNP, -SSA/SSB.

Routine blood chemistry and urinalysis were also performed at the first visit and at regular time intervals during follow-up.

Survival rates

During 1999 the vital status of all patients lost to follow-up was established by contacting the patients themselves or relatives, their primary care physician, or the municipal death registry.

For patients known to have died, hospital records, autopsy reports, or death certificates were examined, when possible, to establish the date and cause of death. On the whole, 90.4% of patient accountability was determined at the end of the study.

For those patients with ascertained cause of death, each death was classified as definitely SSc-related (death caused by organ insufficiency, such as renal crisis, or by a manifestation attributable to no other causes or predisposing factor than SSc, for example severe lung fibrosis), possibly SSc-related (death caused by a manifestation either aggravated by SSc-related organ involvement, such as pneumonia complicating severe lung fibrosis, or occurring with increased frequency in SSc, for example lung cancer), and unrelated to SSc organ injury or treatment.

Statistical analysis

Cumulative survival rates were computed by the Kaplan-Meier method (23), and the difference between survival curves by the Mantel-Cox (log-rank) statistics using BMDP P1L (5). Survival curves were compared to expected deaths in the age- and sex-matched general Italian population (records from Italian ISTAT register).

To identify potentially important prognostic variables, the individual effect of some variables on survival was evaluated with the use of the Cox proportional hazard regression model using BMDP P2L (5, 9). According to a stepwise selection process, variables were entered, or removed, from the regression equation on the basis of a computed significance probability (maximized partial likelihood ratio). Univariate analysis by Cox model and multivariate analysis were also performed separately for each of the independent variables. We examined the independent relationship to mortality risk of 6 main clinico-epidemiologic variables (patient age, sex, skin subsets, lung, heart, and kidney involvement) and 5 serologic parameters (erythrocyte sedimentation rate [ESR], hemoglobin, ACA, anti-Scl70, and ANoA). The hazard ratio for each independent variable was expressed as the exponential of the coefficient of the variable in the hazard equation.

Moreover, comparisons between variables were made using the chi-square test, with the Yates correction where appropriate. The unpaired 2-tailed Student t-test with the Bonferroni correction was used for multiple comparisons. A p value < 0.05 was considered significant.

Results

Demographic and clinical features of 1,012 Italian patients evaluated at the beginning and at the end of follow-up (mean, 7.1 yr $\pm$ 5.7 SD) are shown in Table 3. At the last evaluation, 636 (62.8%) patients were alive, 279 (27.6%) were known to have died, and 97 (9.6%) were considered lost to follow-up. These latter showed the same clinico-serologic characteristics of the 915 patients evaluated for survival study. The female/male ratio rose from 7.8 of the entire SSc population at first visit to 10.4 of the surviving 636 patients. At the time of diagnosis lcSSc was the most frequent cutaneous subset; its rather high prevalence was significantly more pronounced at the end of follow-up ($p < .01$). Similarly, the prevalence of various clinical features referring to both living and deceased patients ($n = 915$) significantly increased, with the exception of Raynaud, calcinosis, and renal involvement; only arthritis was less frequently observed.

Table 4 shows the distribution of the main clinico-epidemiologic features among different SSc cutaneous subsets at diagnosis. A relatively higher percentage of male patients was observed in both icSSc and dcSSc than lcSSc ($p < .001$); disease duration calculated from SSc onset was inversely correlated with the extent of skin sclerosis ($p < 0.001$). In icSSc and dcSSc several clinical manifestations were found significantly more frequently—in particular, hypermelanosis, skin ulcers, arthritis, and esophageal and lung involvement (see Table 4)—while sicca syndrome was more commonly associated with lcSSc. The rather high prevalence of various clinical symptoms observed in icSSc and dcSSc was mirrored by the significantly higher mortality rate observed in the same subsets compared to lcSSc ($p < 0.001$).

SSc-related autoantibodies were evaluated during the last 2 decades in three-quarters of patients ($n = 755$); the prevalence of anti-Scl70, ACA, and ANoA in the whole SSc series and their correlation with clinical features are reported in Table 5. At least 1 serologic marker (anti-Scl70, and/or ACA, and/or ANoA) was detected in 89% of patients; anti-Scl70 and ACA were mutually exclusive with the exception of 7 subjects showing both autoantibodies in the same serum sample. On the contrary, 30% of ANoA-positive patients also had serum anti-Scl70 or ACA. Disease duration was comparable among 3 serologic patient subsets. While ACA were rather frequent in females and in lcSSc, AnoA and mostly anti-Scl70 were more

TABLE 3. Clinico-epidermiologic features of 1,012 Italian patients with SSc*

	Beginning of Follow-Up	End of Follow-Up	p Value†
Number of patients	1,012	636 (62.8%)	
Patients deceased	—	279 (27.6%)	
Patients lost to follow-up	—	97 (9.6%)	
Female/male ratio	7.8	10.4‡	
Mean age (yr)	50.5 ± 13.8	57.5 ± 13.2	
Mean disease duration (yr)	5.1 ± 7.3	12.2 ± 9.0	
Mean follow-up (yr)	0	7.1 ± 5.7	
Limited cutaneous SSc	56	64‡	
Intermediate cutaneous SSc	27	22‡	.01
Diffuse cutaneous SSc	17	14‡	
Hypermelanosis	40	48	.001
Calcinosis	21	22	NS
Teleangectasias	69	79	.001
Skin ulcers	48	54	.01
Raynaud phenomenon	96	94	NS
Sicca syndrome	33	44	.001
Arthritis	19	12	.001
Esophageal involvement (X-ray)	60	68	.001
Lung involvement	60	81	.001
Heart involvement	30	35	.001
Renal involvement	7	10	NS

Abbreviations: SSc = systemic sclerosis, NS = not significant.

*Except where otherwise indicated, values are percentages.

†Comparison between the percentages of symptoms observed at the first (n = 1,012) and the last (n = 915, alive + deceased) evaluation (chi-square with continuity correction).

‡Referred to 636 SSc patients still alive at the end of follow-up;

commonly found in icSSc and dcSSc. In general, the presence of main organ involvement did not correlate with serum autoantibodies; only calcinosis and sicca syndrome were significantly more frequent in ACA-positive, and hypermelanosis in ANoA-positive, patients. It is noteworthy that the number of deceased patients was significantly lower in ACA compared to anti-Scl70 or ANoA seropositives.

Causes of death were definitely ascertained in 170 of 279 deceased patients (Table 6). A higher percentage of deaths was observed in males than in females (38% vs 26%; $p < .05$). Heart and lung involvement,

TABLE 4. Cutaneous SSc subsets and clinico-epidemiologic features at diagnosis*

	a lcSSc (n = 565)	b icSSc (n = 270)	c dcSSc (n = 177)	a vs b p Value	a vs c p Value	b vs c p Value
Female/male ratio	12.3	9.8	2.8	NS	.001	.001
Mean disease duration (yr)†	7.0 ± 9.4	4.6 ± 10.9	2.2 ± 4.0	.001	.001	.001
Hypermelanosis	31	49	56	.001	.001	NS
Calcinosis	22	20	20	NS	NS	NS
Teleangectasias	69	72	66	NS	NS	NS
Skin ulcers	43	57	51	.001	NS	NS
Raynaud phenomenon	96	97	94	NS	NS	NS
Sicca syndrome	39	24	24	.001	.001	NS
Arthritis	16	25	22	.01	NS	NS
Myositis	6	5	4	NS	NS	NS
Esophageal involvement	55	65	69	.05	.01	NS
Lung involvement	53	65	71	.01	.001	NS
Heart involvement	23	25	32	NS	.05	NS
Renal involvement	6	7	12	NS	.05	NS
Deceased patients (no.)	19	35	43	.001	.001	NS

Abbreviations: SSc = systemic sclerosis; lcSSc = limited cutaneous scleroderma; icSSc = intermediate cutaneous scleroderma; dcSSc = diffuse cutaneous scleroderma; NS = not significant.

*Except where otherwise indicated, values are percentages.

†Calculated from disease onset.

TABLE 5. Correlation between SSc-related autoantibodies and clinico-epidemiologic features*

	a anti-Scl70+	b ACA+	c ANoA+	a vs b p Value	a vs c p Value	b vs c p Value
Percentage of total SSc series	36	39	20			
Female/male ratio	7.9	17.1	8.8	.02	ns	>.05
Mean disease duration (yr)†	5.2 ± 7.5	5.1 ± 7.9	5.2 ± 7.8	ns	ns	ns
Cutaneous subsets†						
Limited cutaneous SSc	25.3	53	12.8	.001	.001	.001
Intermediate cutaneous SSc	51.3	21.8	22.8	.001	.001	ns
Diffuse cutaneous SSc	58.6	11.3	17.5	.001	.001	ns
Clinical features‡						
Hypermelanosis	38	31	48	ns	>.05	.001
Calcinosis	16	26	16	.01	ns	.02
Teleangectasias	69	69	71	ns	ns	ns
Skin ulcers	51	42	50	>.05	ns	ns
Raynaud phenomenon	96	98	97	ns	ns	ns
Sicca syndrome	34	44	31	.05	ns	.01
Arthritis	17	14	22	ns	ns	.05
Myositis	3	4	6	ns	ns	ns
Esophageal involvement	70	68	68	ns	ns	ns
Lung involvement	61	58	61	ns	ns	ns
Heart involvement	19	23	24	ns	ns	ns
Renal involvement	7	7	2	ns	ns	>.05
Deceased patients (%)	20	11	24	.01	ns	.001

Abbreviations: SSc = systemic sclerosis; ACA = anti-centromere; ANoA = anti-nucleolar autoantibodies.
*Except where otherwise indicated, values are percentages.
†At diagnosis.
‡Evaluated at the end of follow-up.

alone or in association, were the most frequent complications (69%) affecting the overall disease outcome. Other important but less frequent causes of death were cancer and severe renal involvement.

Survival rates

At the first clinical evaluation the 3 SSc series show a comparable composition with regards to patient mean age, sex, and cutaneous subsets. However, different 10th year survival rates were observed among the 3 patient series. Worse cumulative survivals were observed in older SSc series with regards to the year of beginning of the follow up; in particular, the Napoli series showed 63% survival, Pisa 70.4%, and Padova 78.2%. When calculated only for patients recruited after 1985 these differences were less pronounced (72%, 76%, and 82%, respectively).

TABLE 6. Causes of death

No. of patients deceased	279/915	(30.4%)
Females/males	5.3	(235/44)
Causes of Death	No.	(%)
Unknown	109	
Known	170	
Heart involvement	62	(36)
Lung involvement	40	(24)
Heart + lung involvement	15	(9)
Cancer	25	(15)
Kidney involvement	21	(12)
Miscellaneous	7	(4)
SSc-related	36%	
Possibly SSc-related	52%	
Not SSc-related	12%	

The results of the survival study are summarized in Table 7. Cumulative survival of the whole SSc series of 1,012 patients (Figure 4), calculated from the time of diagnosis, showed an almost constant decrease, with rates of 69.2% and 45.5% at the 10th and 20th year, respectively. The observed survival rates were significantly lower than those expected in the Italian age- and sex-matched general population ($p < .00001$). When calculated from disease onset, a significantly higher 10th-year survival was found (87.8% vs 69.2; $p < .0001$; see Table 7). Survival from disease onset was also calculated in those patients with disease duration ≤2 years, recruited after 1985. In this particular subgroup the 10th-year survival from disease onset was comparable to that observed from diagnosis in the whole SSc series (76.9% vs 76.8%; see Table 7 and Figure 9). The prognostic relevance of patient age at the time of disease onset was evaluated by calculating survival rates in 3 subgroups of patients aged ≤35 years, from 36 to 50 years, and ≥50 years. The 10th-year survivals observed among these subgroups were 79.6%, 71.6%, and 60.5%, respectively ($p < .0001$), significantly lower than those expected in age- and sex-matched groups from the Italian general population ($p < .00001$). Moreover, male patients had a worse prognosis than females ($p < .00001$; Figure 5); both male

TABLE 7. Survival rates in different patient subsets

	10th-Year Survival Rate (%)	p Value
Cumulative from diagnosis	69.2	.0001
Cumulative from SSc onset	87.8	
SSc duration ≤2/>2 yr*	76.9/92.8	.00001
Patients aged ≤35/36–50/>50 yr	79.6/71.6/60.5	.0001
Male/female	53.2/71.6	.00001
Limited/intermediate/diffuse	78.3/65.5/52.2	.00001
Limited/diffuse	75.1/53.4	.00001
Raynaud duration ≤1/>1 yr	67.9/73.4	.0164
Lung involvement +/−	64.9/80.6	.00001
Heart involvement +/−	59.1/77	.00001
Renal involvement +/−	34.8/74.6	.00001
Lung & heart & renal involvement +/−	12.6/86.5	.00001
Anti-Scl70‡ +/−	72.2/80.8	.0525
ACA‡ +/−	85.9/72.7	.0004
ANoA‡ +/−	72.6/80.3	NS
Patients recruited 1955–85/1986–99	60.6/76.8	.0001

*Survival calculated from disease onset in patients recruited after 1985.
‡Survival calculated from diagnosis in patients recruited after 1985.

and female SSc patients showed a significantly lower survival compared to the corresponding groups from the general population. The extent of cutaneous sclerosis was significantly correlated with survival ($p < .00001$). Moreover, the survival curve of icSSc was equidistant from both the lcSSc and dcSSc subsets (Figure 6). Using the 2-cutaneous subset classification, statistically different 10th-year survival rates were again observed for lcSSc and dcSSc ($p < .00001$).

In patients with Raynaud duration ≤ or >1 year, at the time of disease onset, significantly different 10th-year survival rates calculated from diagnosis were observed (67.9% vs 73.4%, $p < .0164$).

The presence of main organ involvement (lung, heart, and kidney) was associated with significantly lower survival rates; the worst 10th-year survival rate was observed for patients with renal involvement and for a group of 21 patients with simultaneous

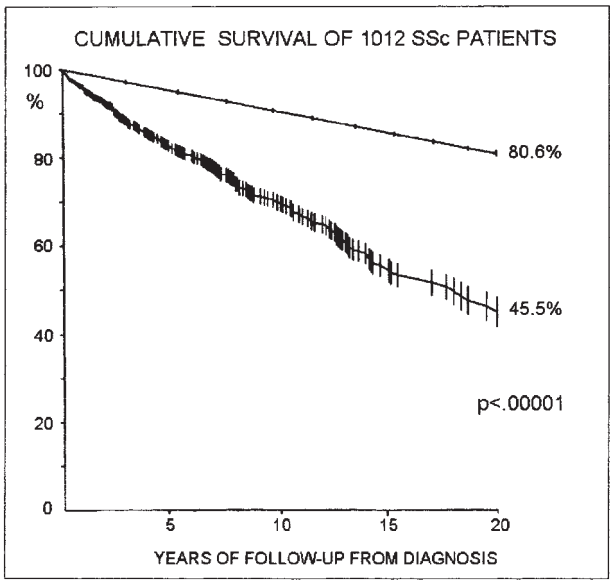

FIG. 4. Cumulative survivals at 10th and 20th year (69.2% and 45.5%, $p < .00001$) from diagnosis in 1,012 SSc patients compared to expected survival (80.6%) in the Italian general population ($p < .00001$).

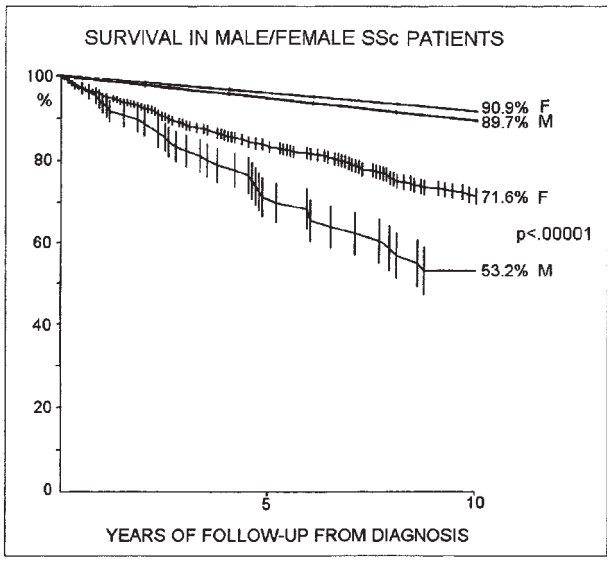

FIG. 5. Survival rates in female and male patients (71.6% vs 53.2%, $p < .00001$) were significantly lower than expected survival rates ($p < .00001$).

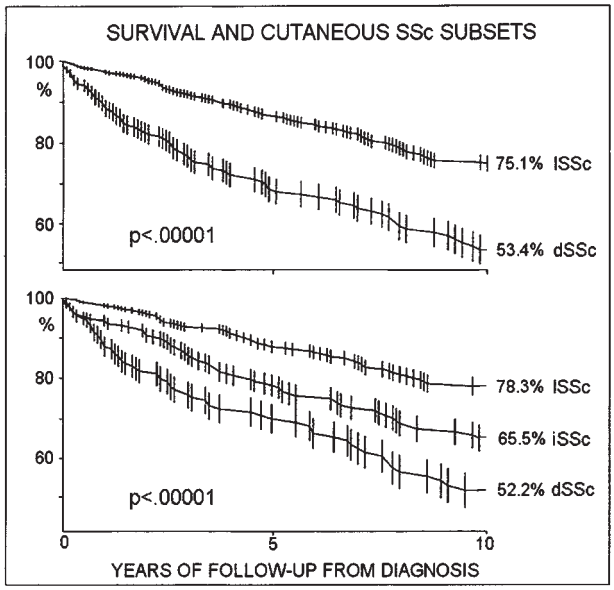

FIG. 6. Survival rates in cutaneous SSc subsets classified according to the 2-subset model (limited [lSSc] and diffuse [dSSc]) or the 3-subset model (limited [lSSc], intermediate [iSSc], and diffuse [dSSc]).

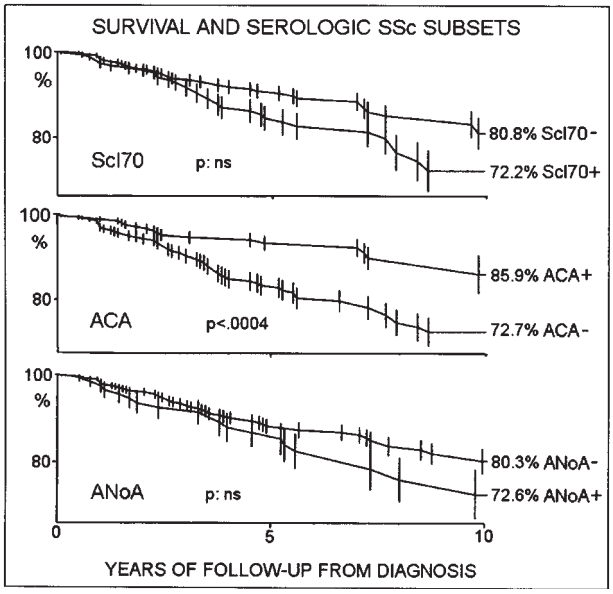

FIG. 8. Survival rates in patients with (+) or without (-) serum autoantibodies (Scl70: anti-Scl70; ACA: anti-centromere; ANoA: anti-nucleolar).

lung, heart, and kidney involvement (Figure 7; see Table 7). No statistically significant differences were observed in SSc subsets classified according to presence/absence of serum anti-Scl70 or ANoA, while ACA-positive patients were characterized by a better prognosis compared with ACA-negative patients (Figure 8; see Table 7).

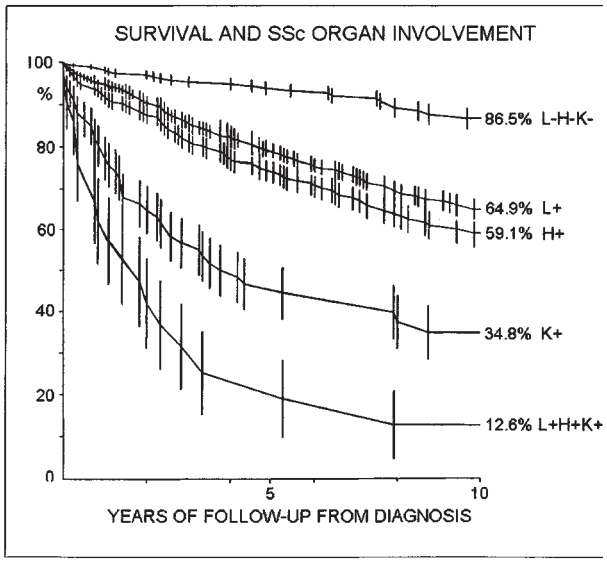

FIG. 7. Survival rates in different visceral organ involvement (L: lung; H: heart; K: kidney). The presence (+) of visceral organ involvement was associated with significantly worse survival rates compared with the absence (-) thereof; see also Table 7.

The results of univariate and multivariate survival analysis by Cox proportional hazards model (Table 8) further support some of the above prognostic findings obtained by Kaplan-Meier survival curves. We analyzed 6 main variables (patient age, sex, skin subsets, lung, heart, and kidney involvement) in a large group of 914 SSc patients (other variables were frequently missing values, so they were not analyzed in this group). All variables were associated with increased risk of mortality at univariate analysis, often confirmed by multivariate analysis. In particular, by means of univariate analysis, for every increase in year of age there was a 4% increase in mortality risk; male gender showed an 82% increase mortality; lung, heart, and kidney involvement a 102%, 112%, and 340% increase, respectively. All cutaneous subsets showed an increased mortality risk, which was correlated to the extent of skin sclerosis: in dcSSc the excess of mortality was 3 times that observed in lcSSc. The analysis of 529 patients, including serologic parameters, demonstrated that increased ESR at diagnosis (>25 mm/h) was associated with 93% excess mortality, while the presence of serum ACA was associated with a lower mortality risk (see Table 8).

Finally, the survival study focused on the possible variations of SSc outcome during the last few decades; in this respect, survival rates were evaluated by subdividing the whole SSc series in 2 groups according to different time intervals of enrollment.

TABLE 8. Relationship between SSc mortality and risk factors by univariate and multivariate analysis

	529 SSc Patients				914 SSc Patients			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age/year	1.07	1.05–1.10	1.08	1.05–1.10	1.04	1.03–1.06	1.04	1.03–1.06
Sex								
Male	1.0		—		1.82	1.24–2.66	—	
Female	1.0				1.0			
Skin involvement								
lcSSc	1.46	1.08–1.98	1.74	1.26–2.40	1.71	1.44–2.03	1.70	1.43–2.40
icSSc	2.13		3.03		2.91		2.88	
dcSSc	3.10		5.27		4.97		4.89	
Lung involvement								
Present	2.23	1.22–4.06	2.52	1.34–4.73	2.02	1.47–2.78	1.68	1.21–2.33
Absent	1.0				1.0			
Heart involvement								
Present	1.0		—		2.12	1.59–2.82	1.46	1.09–1.96
Absent	1.0				1.0			
Kidney involvement								
Present	8.05	4.47–14.5	8.10	4.33–15.1	4.40	3.08–6.29	3.76	2.61–5.43
Absent	1.0				1.0			
ESR mm/h								
>25	1.93	1.16–3.23	—		ND			
≤25	1.0							
Hb g/dL								
≤12	1.0		—		ND			
>12	1.0							
ACA								
Present	0.56	0.31–1.01	—		ND			
Absent	1.0							
Anti-Scl70								
Present	1.0		—		ND			
Absent	1.0							
ANoA								
Present	1.0		—		ND			
Absent	1.0							

Abbreviations: See previous tables. ND: not done due to the high number of missing values, CI = confidence intervals; ESR = erythrocyte sedimentation rate; Hb = hemoglobin.

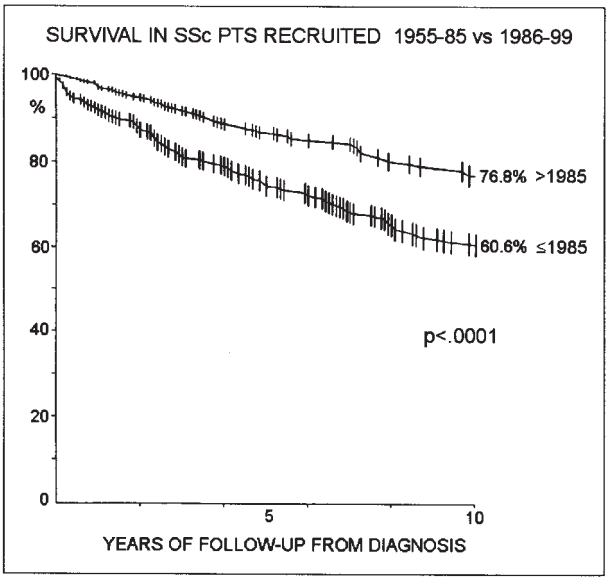

FIG. 9. Cumulative survival rates in patients recruited during 1955–1985 and 1986–1999, respectively.

In particular, patients recruited from 1986 to 1999 showed a significantly higher 10th-year survival rate compared with those recruited from 1955 to 1985 (76.8% vs 60.6%; $p < .0001$) (Figure 9; see Table 7).

The 10th-year survival rate observed in the present SSc population was comparable to the mean value of survival rates found in other SSc series reported during the last decade (69.2% vs 72.0%; Table 9). In this respect, the mean survival rate observed in the older reports was significantly lower than that found in more recent studies (1–3, 6, 10–14, 16, 20, 24, 25, 27, 29, 33, 37) (see Table 9).

Discussion

This multicenter, retrospective follow-up study evaluated clinico-epidemiologic and prognostic parameters in a large Italian SSc patient population. A number of demographic and clinical features confirmed in part the observations of previous reports (1, 2, 6, 11–14, 20, 28, 31). In particular, the disease more frequently affects middle-aged females; limited cutaneous involvement represents the most frequent clinical variant; and SSc multisystem involvement shows a significant progression over follow-up. The prevalence of many features such as lung, heart, and esophageal involvement was significantly increased at the last patient evaluation; consequently, a fatal outcome was recorded in over one-quarter of patients. SSc could be directly or indirectly responsible for death in the majority of cases; cardiopulmonary involvement and cancer were the most frequent causes of death, while severe renal involvement was observed in a relatively small number of deceased patients. The prevalence of nephropathy in our SSc patients and its relative percentage among causes of death are smaller compared to other series from Northern Europe or the United States (1, 14); while a

TABLE 9. Survival studies in systemic sclerosis patients

First Author, Year (ref.)	Country	Referral Center	Recruitment Period	No. of Patients	10th-year Survival (%)
Older Studies					
Tuffanelli, 1961 (33)	US	Dermatology	1935–58	727	59
Bennett, 1971 (3)	UK	Rheumatology	1947–70	67	40
Medsger, 1971 (20)	US	Rheumatology	1955–70	309	35
Rowell, 1976 (27)	UK	Dermatology	1960–75	84	74
Altman, 1991 (1)	US	Rheumatology	1973–77	264	42
Barnett 1988 (2)	Australia	Rheumatol	1953–78	113	55
Eason 1981 (10)	New Zealand	Internal Medicine	1970–80	47	42
Wynn 1985 (37)	US	Internal Medicine	1970–80	64	51
Giordano 1986 (12)	Italy	Rheumatology	1963–83	90	32
More Recent studies					
Ferri 1991 (11)	Italy	Rheumatology	1972–89	151	65
Lee 1992 (16)	Canada	Rheumatology	1979–90	237	61
Simeon 1997 (29)	Spain	Internal Medicine	1980–90	72	85
Bryan 1996 (6)	UK	Rheumatology	1982–92	283	75
Nagy 1997 (24)	Hungary	Internal Medicine	1982–93	171	70
Nishioka 1996 (25)	Japan	Dermatology	1974–94	496	82
Hesselstrand 1998 (13)	Sweden	Rheumatology	1983–95	249	69
Jacobsen 1998 (14)	Denmark	Rheumatology	1960–96	344	71
Present report	Italy	Rheumatology	1955–99	1,012	69
Mean survival in older studies					47.8 ± 13.3
Mean survival in more recent studies					72.0 ± 7.60
					$p < .0005$

comparable prevalence of renal involvement was reported in other patient series from the Mediterranean area (29, 35). Besides other unknown genetic and/or environmental cofactors, the discrepancy in the prevalence of renal involvement among various SSc patient populations might be correlated to different climatic conditions, potentially relevant for the development of this complication.

Survival study demonstrated a statistically higher mortality in SSc patients compared to the Italian general population; the percentage of surviving patients showed an almost linear decrease during a 20-year follow-up period. The worst prognostic parameters were the male gender, a wide extent of skin sclerosis, and the presence of main visceral organ involvement, that is, heart, lung, and kidney. Another useful prognostic indicator was the time interval between the appearance of Raynaud phenomenon and the onset of scleroderma: a shorter Raynaud duration at the disease onset significantly correlated with a worse survival. With regards to the serologic markers, a relationship between the presence of ACA or anti-Scl70 and the extent of skin sclerosis was observed; namely, ACA were significantly more frequent in lcSSc, and anti-Scl70 in both icSSc and dcSSc subsets. More interestingly, the survival study suggested a "protective" role of ACA; as observed in previous studies, a better prognosis was found in ACA-positive individuals (15, 17, 19, 28, 31). On the contrary, patients with anti-Scl70 and/or ANoA showed a significantly higher percentage of deaths compared to ACA seropositives.

The analysis by Cox proportional hazards model further stressed the prognostic relevance of the above parameters. An increased mortality risk was correlated with male gender, extent of skin sclerosis, presence of lung, heart, and renal involvement; comparable findings have been found in other patient series from the United States and the United Kingdom (1, 7).

However, some important differences emerged with regards to the prevalence of clinico-serologic features and survival rates among various series from different countries, as well as between the present SSc series and previous studies (1–3, 6, 10, 13, 14, 16, 20, 24, 25, 27, 29, 33, 37; see Table 9). It is often difficult to explain these discrepancies; racial and/or environmental etiopathogenetic factors, and not secondarily different methodologic approaches, among referral centers should be taken into account.

There is unanimous agreement to consider the extent of skin sclerosis as the most useful clinico-prognostic tool (2, 11, 12, 17–19, 28, 31). In the absence of other more specific and sensible clinico-serologic parameters, the SSc classification in cutaneous subsets represents a feasible and useful indicator, particularly at the initial patient assessment. The present study further supports our previous observation suggesting a better discriminating power of the 3-subset classification (11, 12). In fact, patients with lcSSc, corresponding to sclerodactyly, showed a significantly lower mortality rate with a better 10th-year survival compared to patients with either icSSc or dcSSc. These latter 2 subsets shared a number of clinico-serologic features, that is, the prevalence of skin ulcers, arthritis, esophageal and lung involvement, and anti-Scl70 seropositivity, together with the percentage of deceased patients. On the contrary, the presence of sclerodactyly, with or without sclerosis of the neck and/or face, seems to identify a subgroup of patients with the best prognosis. For future clinical investigations, a uniform classification of SSc patients should be adopted by different referral centers. Following either the 2- or 3-subset model, it might be opportune to group subjects with very limited skin sclerosis (sclerodactyly) in a subset with peculiar clinico-serologic and prognostic features.

Compared with other connective tissue diseases, SSc is characterized by a higher mortality rate. The fatal outcome may be the consequence of severe single organ injury, mainly kidney, lung, or heart, or more often it may be the result of the combined involvement of various internal organs. Thus, a single clinical manifestation, even the extent of cutaneous sclerosis, is not necessarily a valid prognostic indicator in a given patient. In this respect, survival studies on large SSc series can give us new insights on the prognostic relevance of different clinico-serologic parameters. However, various authors have pointed out the difficulties in interpreting survival data from different patient populations because of their frequent heterogeneity (6, 13, 28). The correct approach to retrospective survival studies is still controversial. Two kinds of problems remain to be resolved: the modality of patient selection and the survival calculation. SSc is a relatively rare disorder, characterized by a wide spectrum of clinical symptoms; very mild to moderate clinical variants are rather common. It is likely that the more severe cases are concentrated in referral centers; consequently, the actual mortality from scleroderma, evaluated in patients attending specialist centers, may be overestimated. In addition, the correct evaluation of the natural history of the disease implies the calculation of the disease duration from disease onset to death. However, this approach could be misleading. First, there is a long delay between the clinical onset and the diagnosis, especially for slow progressive SSc variants; in these cases it is often arbitrary to name a date for the disease onset, even for the patients themselves. Moreover, this modality introduces an important methodologic error, the so called immortality bias (18); patients referred to specialist centers did not represent the entire SSc population, but a surviving cohort. Therefore, the survival calculated from dis-

ease onset invariably underestimated the true mortality from SSc. In recent years, an increasing number of patients with early SSc have been referred to Italian specialist centers due to the better knowledge of the disease by general practitioners and patients themselves, as well as the wide diffusion of some diagnostic tools, such as capillaroscopy. In the future, prospective studies on patient populations referred early in the course of the disease could minimize the above-mentioned problems.

In the present study we have attempted to overcome these difficulties, at least in part, by evaluating the survival in those patients with early SSc (<2 years), referred to the 3 Italian centers after 1985. This particular subgroup of patients, whose recalled date of disease onset was sufficiently reliable, could better reflect the actual composition of the SSc spectrum. Surprisingly, the 10th-year survival calculated from disease onset in this subgroup (76.9%) was similar to that obtained from diagnosis in the whole SSc series (76.8%). It is difficult to explain the significance of this latter observation. One possible interpretation could be that cumulative SSc survival calculated from diagnosis is burdened with 2 opposite factors: the concentration in referral centers of a population with more severe disease and rather high mortality, on the 1 side, and the presence of a "surviving" SSc cohort with better prognosis, on the other side. Due to the above counterbalancing factors, the survival rates calculated from diagnosis, as usually reported in retrospective studies, might sufficiently reflect the actual outcome of the disease.

Different survival rates observed in our 3 patient series showed a north-south gradient. A possible role of genetic and/or environmental cofactors in different series can be reasonably excluded on the basis of the following considerations. Compared to the Padova series, patients in the Pisa and especially the Napoli series had been recruited over a wider time interval, including the 1950s and 1960s, when a relatively higher percentage of patients with more severe SSc were referred to specialist centers. If evaluated only in patients referred to the 3 centers after 1985, comparable 10th-year survival rates were demonstrated among the 3 SSc populations. As mentioned above, more severe SSc variants were probably concentrated in referral centers during the last 4–5 decades. This possibility could be indirectly supported by the better survival rates medially observed in more recent studies compared with previous reports. The improved prognosis among various SSc patient populations seems to be independent of different racial and/or environmental pathogenetic cofactors and/or different methodologic approaches (1–3, 6, 10–14, 16, 20, 24, 25, 27, 29, 33, 37). It is possible to hypothesize that the improved SSc outcome, largely observed during the last years, could be related to a wider patient recruitment at specialist centers, which better reflects the entire scleroderma spectrum. Moreover, the possible contribution of recently available treatments also should be taken into account (4, 19, 30, 36). The treatment of SSc is commonly divided into 2 broad headings: treatment of organ manifestations, that is, scleroderma renal crisis, esophageal, lung or heart involvement, and digital ulcerations, and disease-modifying therapy aimed at influencing the pathogenetic process (Table 10). Despite the present lack of any drug or combination of drugs clearly effective as disease-modifying therapy (4), some significant advances have been reached in the last 20 years in treating organ-based manifestations (4). In this respect, some studies have pointed out the efficacy of cyclophosphamide in the treatment of fibrosing alveolitis in its early inflammatory stage.

TABLE 10. Treatment of systemic sclerosis

Proposed Disease-modifying Therapies	Organ Manifestation Treatments
Antilymphocyte globulin	Raynaud phenomenon ± active skin ulcers
Antithymocyte globulin	Ca-channel blockers, iloprost, aspirin
Autologous stem cell transplantation	Scleroderma renal crisis
Azathioprine	ACE inhibitors, dialysis
Clorambucil	Cardiac involvement
Colchicine	ACE inhibitors, antiarrhythmics, pacemaker, steroids (pericarditis)
Cyclophosphamide	Pulmonary hypertension
Cyclosporin A	Iloprost, prostacyclin, oral anticoagulation
D-penicillamine	Lung involvement
Interferon-alpha	Cyclophosphamide, oxygen, lung transplant
Interferon-gamma	Esophageal, intestinal involvement
Methotrexate	Prokinetics, omeprazole, antibiotics
Photoapheresis	Articular involvement, myositis
Plasmapheresis	Low-dose steroids
	Skin sclerosis
	Emollients, exercises

Abbreviations: ACE = angiotension-converting enzyme inhibitors.

The extreme variability of SSc prevents us from identifying a treatment useful for all patients. Actually, the therapy must be tailored to the individual patient depending on the extent and severity of organ involvement and the pathophysiologic stage of the disease, that is, active-evolutive or inactive-stable SSc.

Summary

In this multicenter, retrospective study we evaluate the clinico-epidemiologic and prognostic features of a large Italian systemic sclerosis (SSc) series (1,012 patients, 897 females and 115 males; mean age at presentation, 50.5 yr ± 13.8 SD; mean follow-up, 7.1 yr ± 5.7 SD) recruited between 1955 and 1999 at 3 university-based rheumatology units, from the north (University of Padova), center (University of Pisa), and south (University of Napoli) of Italy. Limited cutaneous SSc was the most frequent subset with the best prognosis independent of the classification used, based on skin sclerosis extent (2- or 3-subset models). The percentages of various organ involvement significantly increased at the last patient evaluation. The progression of the disease during follow-up was mirrored by the constant decrease in the cumulative survival rates (Kaplan-Meier method) calculated at the 10th and 20th year from diagnosis (69.2% and 45.5%, respectively, $p < .00001$); the observed SSc survival rates were significantly lower than those expected in the Italian general population ($p < .00001$).

Among SSc patients, significantly worse prognosis was observed in the diffuse cutaneous subset ($p < .00001$), in male gender ($p < .00001$), and in patients with lung ($p < .00001$), heart ($p < .00001$), and renal involvement ($p < .00001$). A shorter duration of Raynaud phenomenon before the scleroderma onset was correlated with worse outcome ($p < .0164$). With regards to serologic markers, the presence or absence of anti-centromere antibody was an important prognostic indicator (85.9% vs 72.7% 10th-year survival, respectively; $p < .0004$). Univariate and multivariate analysis by Cox proportional hazard regression model further confirmed the results of survival study: the mortality risk was significantly increased in male patients; in patients with diffuse cutaneous SSc; in patients with lung, heart, and kidney involvement; and in patients with abnormally high erythrocyte sedimentation rate (ESR) (>25 mm/h) evaluated at patient enrollment. Thirty percent of patients died during the follow-up period; the most frequent causes of death were cardiac (36%) and lung (24%) involvement, and cancer (15%). Deaths were definitely or possibly related to SSc in 36% and 52% of cases, respectively. Renal involvement was a relatively rare complication in Italian SSc patients; comparable features were observed in other SSc populations from the Mediterranean area.

Patients recruited after 1985 showed a significantly better 10th–year survival rate compared with subjects referred before 1985 (76.8% vs 60.6%, $p < .0001$). Comparable survival rates have been reported in recent studies on SSc series from other countries. This finding could be related to the wider recruitment of mild-to-moderate clinical variants at specialist centers, which better reflects the entire scleroderma spectrum, and, not secondarily, to the possible contribution of recently available therapies.

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