The presence of small joint contractures is a risk factor for survival in 439 patients with systemic sclerosis

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ABSTRACT

Objective. *Analysis of risk factors and mortality of 439 patients with systemic sclerosis (SSc) in a tertiary care centre.*

Methods. *The mean follow-up time was 8.4±5.6 years. Lost to follow-up rate was 6.4%. Female to male ratio was 366 to 73. Two hundred sixty patients had limited and 179 diffuse cutaneous SSc (dcSSc). A standard protocol including musculoskeletal examinations was used for the assessment of patients.*

Results. *By Kaplan-Meier analysis the overall 5-, 10- and 15 year survival were 88.2%, 79.9% and 73.6%, respectively. Univariate analysis showed that dcSSc, male gender, presence of small joint contractures, pulmonary interstitial, cardiac, oesophageal involvement, scleroderma renal crisis, arterial hypertension, anti-topoisomerase antibody, anaemia, hypalbuminaemia, coexistent malignancies and elevated erythrocyte sedimentation were associated with poor survival. Lack of giant capillaries, avascular zones or neoangiogenesis on capillaroscopy, and presence of anti-centromere antibodies were associated with favourable outcome. Multivariate regression analysis showed presence of small joint contractures, history of arterial hypertension, male gender, diffusing capacity of carbon monoxide <50%, right ventricular pressure >40 mmHg on echocardiography, less than 50% ejection fraction, anti-topoisomerase I positivity, anaemia, and serum albumin concentration < 35 g/l as well as current or history of coexistent malignancy were independent poor prognostic factors.*

Conclusion. *In addition to well-known factors predicting poor outcome in SSc, the presence of small joint contractures was a newly identified independent risk factor of mortality. Our data also confirmed a recent finding showing that history of arterial hypertension was also a poor prognostic factor.*

Introduction

Systemic sclerosis (SSc) is characterised by vascular abnormalities, fibrosis and inflammation affecting the skin and numerous internal organs. Previous studies showed that older age at onset (1-22), male gender (1, 4, 8, 10, 12, 15, 16, 18, 20, 21, 23-27), diffuse cutaneous subset (1, 2, 4, 5, 9-12, 14, 15, 19, 20, 22-26, 28), interstitial pulmonary involvement (1, 6, 7, 9, 10, 12, 14-16, 18, 23, 25, 26, 29, 30), decreased FVC and/or DLCO (2-5, 7, 11, 17, 19-22, 27, 30, 31), pulmonary arterial hypertension (1, 2, 4, 10, 13, 19, 20, 23, 25, 26), cardiac (1, 2, 6, 7, 9, 12, 15, 18, 22, 25, 28, 32) and renal involvement (1, 6, 9, 10, 12, 14-20, 22, 25, 27, 32) were associated with poor outcome. Certain gastrointestinal manifestations (9, 16, 22, 27, 30) were also associated with poor prognosis. The presence of contractures (7, 9), electrocardiogram abnormalities (3, 11, 29, 31), including high number of ventricular ectopic beats (30), pigmentation disturbances (9, 22), decreased ejection fraction (20), elevated ESR (3, 7, 9, 11-13, 21, 22, 27, 32), low haemoglobin and/or haematocrit concentration (3, 7, 22, 27), and hypoalbuminaemia (27) were also found to predict a poor outcome. Furthermore, presence of anti-topoisomerase (1-3, 12, 18, 20, 22) autoantibody was associated with poor survival, the presence of anti-centromere antibody (1, 9, 22, 23, 25, 31) was associated with better outcome. Elevated level of other biomarkers including high sensitivity troponin and B-type natriuretic peptides were also associated with poor outcome (30). Certain comorbidities including arterial hypertension (20, 28, 30), and coexistent malignancy (10, 14, 22) were also identi-

fied as poor prognostic factors of SSc. Our previous study also confirmed that a coexistent malignancy was an independent predictor of mortality (22).

The aim of our study was to analyse the survival, causes of death and risk factors affecting mortality in a large series of patients with SSc followed up in a university tertiary care center in Hungary. Known risk factors were confirmed by our analysis and small joint contractures were found to be novel independent risk factors of mortality.

Patients and methods

We enrolled all patients investigated in our tertiary center at least two times between 1995 and 2015. Baseline data were collected prospectively in our database, thus in some cases retrospective data analysis was also performed. Patients lost to follow-up were defined as patients who did not appear in the center for twelve month after their last visit. In order to clarify the reason of the patients' absence in the follow-up, telephone calls were made and letters were sent to patients and if possible to the local GP. University patient database was also checked. The diagnosis based on American College of Rheumatology preliminary classification criteria (33) was found in 469 cases, and only 30 patients were considered lost to follow-up (6.4%).

Causes of death were defined based on last discharge papers, consultation with the patients' GP and autopsy results (available in 20 out of 106 deceased patients). Besides the overall mortality rate, SSc-related death was also defined as a cause of death clearly explained by major organ manifestation(s) of disease and/or the adverse events of the therapy. Causes of death due to coexistent malignancies and organ manifestations caused by scleroderma overlap syndromes were also evaluated. Each cause of death was extensively discussed, and a final agreement of three investigators (GN, GK, LC) were achieved.

Pulmonary interstitial involvement (ILD) was documented in case of fibrosis detected by high resolution computer tomography (HRCT) and concurrent decreased forced vital capacity (FVC<80%). Extensive pulmonary involvement was recorded in case of either the fibrosis affected the upper and middle area of the lungs on HRCT or FVC<50% or honeycombing was detected by HRCT.

Cardiac involvement was recorded if the patient had at least one of the following conditions: decreased ejection fraction <50%, elevated right ventricular pressure detected by echocardiography (>40 mmHg - except in patient with severe pulmonary involvement), relaxation disorder (defined by the cardiologist evaluation based on E/A ratio), abnormal electrocardiogram (ECG) (arrhythmia, conduction disturbances, brady- or tachycardia; heart rate consistently <60/min or higher than 85/min confirmed by cardiologist that it is heart manifestation related). Pulmonary arterial hypertension (PAH) was recorded if elevated mean pulmonary arterial hypertension was verified by right heart catheterisation (RHC). Patients having elevated right ventricular pressure on echocardiography were referred to RHC by the cardiologist based on a standard protocol. The overwhelming majority of patients was examined by the same cardiologist team (34).

Oesophageal involvement was documented if the patient had dysphagia and/or barium-swallowing x-ray showed dys/hypomotility and/or strictures/dilatation. Scleroderma renal crisis (SRC) (including the normotensive form) was defined by the agreement of two experts (GK, LC) based on the available definition (35). Sicca complaints were recorded if the patient was complaining about xerostomia and/or xerophtalmia and it was confirmed with at least one functional test.

Small joint contractures were recorded if range of motion was less than 75% of normal in the metacarpophalangeal and proximal interphalangeal joints evaluated by rheumatologists of our tertiary care center.

Low body weight was defined as the patient's body mass index (BMI) was less than 18, normal if BMI was between 18-25, and higher if it was higher than 25. Systemic arterial hypertension was documented if hypertension was diagnosed previously or diagnosis of hypertension was established simultaneously with SSc. Coexistent malignancy was documented in cases when time between malignancy and SSc onset was maximum 5 years.

Abnormal nailfold capillary pattern was registered in presence of giant capillaries, haemorrhage, capillary loss or signs of neoangiogenesis (36).

Anaemia was recorded in case if haematocrit <33%. Hypoalbuminaemia was recorded if serum albumin levels were less than 35g/l. Elevated erythrocyte sedimentation rate (ESR) was recorded if higher than >30mm/h. Elevated C-reactive protein (CRP) level was recorded if higher than >5 mg/l.

Antinuclear (ANA-Ease ELISA Kit GD74, Alva, United Kingdom), anticentromere (Orgentec, ORG 633, Mainz, Germany) and anti-Scl-70 (Orgentec, ORG 212-24, Mainz, Germany) antibodies were detected by ELISA method. Anti-polymerase III antibodies were detected by immunoblot technique (Euroimmune, DL 1532-1601 G, Mountain Lakes, USA).

For statistical analysis Kaplan-Meier curves and log-rank test were used to determine the survival and factors affecting the survival. Items found to be significant according to univariate analysis were further tested with to Cox proportional hazard model to examine the independent prognostic factors. Fisher's exact test and t-test were performed to compare subgroups, as appropriate. For all analysis v. 16.0 SPSS for Windows was used (Inc., Chicago, IL, USA).

The study was approved by the Regional Ethics Committee (2939/2007). Written informed consent was obtained from patients according to the Declaration of Helsinki.

Results

Survival and risk factor analysis

The median age at onset was 46 years. Diffuse cutaneous SSc (dcSSc) was present in 179 (40.8%) cases. Seventy-three (16.6%) male patients were enrolled. The main clinical characteristics can be seen in Table I.

Coexistent malignancies could be detected in 36 cases; the ratio of limited

Table I. Baseline clinical features of patients.

	n./available (%)
n. of patients	439
Age at onset of Raynaud's phenomenon (median, lower;upper quartile) years	46 (34;55)
Age at the first non-Raynaud's phenomenon (median, lower;upper quartile) years	49 (40;58)
Mean follow-up time from onset of Raynaud's phenomenon (years)	8.42 ± 5.6
Time between onset of Raynaud's phenomenon and enrolment (median, lower;upper quartile) years	3 (0;4)
n. of male patients	73 (16.6)
n. of dcSSc patients	179 (40.8)
Extensive pulmonary interstitial involvement[†]	103 (23.5)
Pulmonary interstitial involvement[††]	236 (53.8)
FVC<80%	72/427 (16.9)
DLCO<70%	216/418 (51.6)
Cardiac involvement[#]	257/439 (58.5)
More than 40 mmHg right ventricular pressure on echocardiography	34/418 (8.1)
Ejection fraction<50%	9/418 (2.1)
Scleroderma renal crisis^	12 (2.7)
Oesophageal involvement[§]	195/433 (45)
Pulmonary arterial hypertension[##]	14/30 (3.2 of all patients)
Sicca complaints[§§]	116 (26.4–Schirmer available 85.6% and saliva measurements in 65.6%)
Small joint contractures~	158 (36)
ACA positivity	113/437 (25.9)
Anti-topoisomerase I positivity	157/437 (35.9)
Anti-RNA polymerase III positivity	31/135 (22.9)
Elevated ESR (>30mm/h)	127/422 (29.4)
Elevated CRP (>5mg/l)	219/424 (51.6)
Low haemoglobin level (male <137g/l; women <120g/l)	131/430 (30.5)
Low haematocrit level (<33%)	45/430 (10.5)
Azotemia (creatinine >100μmol/l)	45/421 (10.6)
Hypalbuminaemia (<35g/l)	27/384 (7)
Coexistent malignancies[**]	36 (8.2)
Concurrent or history of malignancies	54 (12.3)
History of arterial hypertension[*]	175 (39.9)
Diabetes mellitus	26 (5.9)

[††]Pulmonary interstitial involvement (ILD) was recorded in case of fibrosis detected by high resolution computer tomography (HRCT) and concurrent decreased forced vital capacity (FVC<80%).

[†]Extensive pulmonary involvement was recorded in case of either the fibrosis affected the upper and middle area of the lungs on HRCT or FVC<50% or honeycombing was detected by HRCT.

[#]Cardiac involvement was recorded if the patient had at least one of the following items: decreased ejection fraction <50%, elevated right ventricular pressure detected by echocardiography (>40 mmHg-except in patient with severe pulmonary involvement), relaxation disorder (defined by the cardiologist evaluation based on E/A ratio), abnormal electrocardiogram (ECG) (arrhythmia, conduction disturbances, brady- or tachycardia; heart rate consistently <60/min or higher than 85/min confirmed by cardiologist that it is heart manifestation related).

[##]Pulmonary arterial hypertension (PAH) was recorded if elevated mean pulmonary arterial hypertension was verified by right heart catheterisation (RHC).

[§]Oesophageal involvement was recorded if patient had dysphagia and/or barium-swallowing x-ray showed dys/hypomotility and/or strictures/dilatation.

^Scleroderma renal crisis (SRC) (including the normotensive form) was defined by two experts (GK, LC) based on the definition: a new onset of significant systemic hypertension (>150/85mmHg) and decreased renal function (≥30% reduction in estimated glomerular filtration). Normotensive cases were registered if there was no change in blood pressure but other manifestations of SRC occurred.

[*]Systemic arterial hypertension was recorded if hypertension was diagnosed previously or diagnosis of hypertension was established simultaneously with SSc.

~Small joint contractures were recorded if range of motion was less than 75% of normal in the metacarpophalangeal and proximal interphalangeal joints evaluated by rheumatologists.

[§§]Sicca complaints were recorded if the patient was complaining about xerostomia and/or xerophtalmia and it was confirmed with at least one functional test.

[**]Coexistent malignancy was recorded in cases when time between malignancy and SSc onset was maximum 5 years.

cutaneous SSc (lcSSc) to dcSSc patients was 22 to 14 (1.6:1). 29 female and 7 male patients had coexistent malignancies. The mean time between onset of SSc and malignancy was 2.1±1.1 years. Twelve patients had topoisomerase positivity, 10 anti-centromere positivity and 2 RNA Pol III positivity. Out of the 29 female patients with coexistent malignancies, 11 had breast cancer, 5 cervical cancer, 1 colon adenocarcinoma, 4 haematologic malignancies, 2-2 lung and ovarian cancer, 1 endometrial carcinoma, 2 skin cancer (one melanoma and one non-melanoma skin cancer) and 1 multiple malignancy. In the 7 male patients with coexistent malignancies, 3 haematologic malignancies, 1 small cell lung cancer, 1 lung adenocarcinoma, 1 uroepithelial carcinoma and 1 prostate cancer were identified. No statistical difference was revealed on comparison of clinical features of patients with and without coexistent malignancies. Patients with coexistent malignancy had significantly worse survival by univariate analysis compared to those without coexistent malignancy ($p<0.0001$).

The all-cause mortality was 88.2% at 5 years, 80.8% at 10 years, 67.5% at 15 years and 31.6% at 20 years, respectively. When only the SSc related causes of death were taken, the survival rate showed 95.6% at 5 years, 87.5% at 10 years and 74.2% at 15 years, respectively. When fatal outcome caused by overlap syndrome and/or coexistent malignancy was added to the strictly SSc-related causes of death we found 88.1% survival at 5 years, 79.9% at 10 years, 73.6% at 15 years and 63.4% at 20 years (Fig. 1A).

Univariate analysis showed that dcSSc, male gender, presence of small joint contractures, ILD, cardiac involvement, elevated right ventricular pressure on echocardiography, less than 50% ejection fraction and ECG abnormalities, oesophageal involvement, scleroderma renal crisis, history of hypertension, anti-topoisomerase positivity, low haemoglobin, haematocrit and albumin levels, elevated ESR, coexistent and current or previously diagnosed malignancies were associated with poor prognosis. Conversely, the pres-

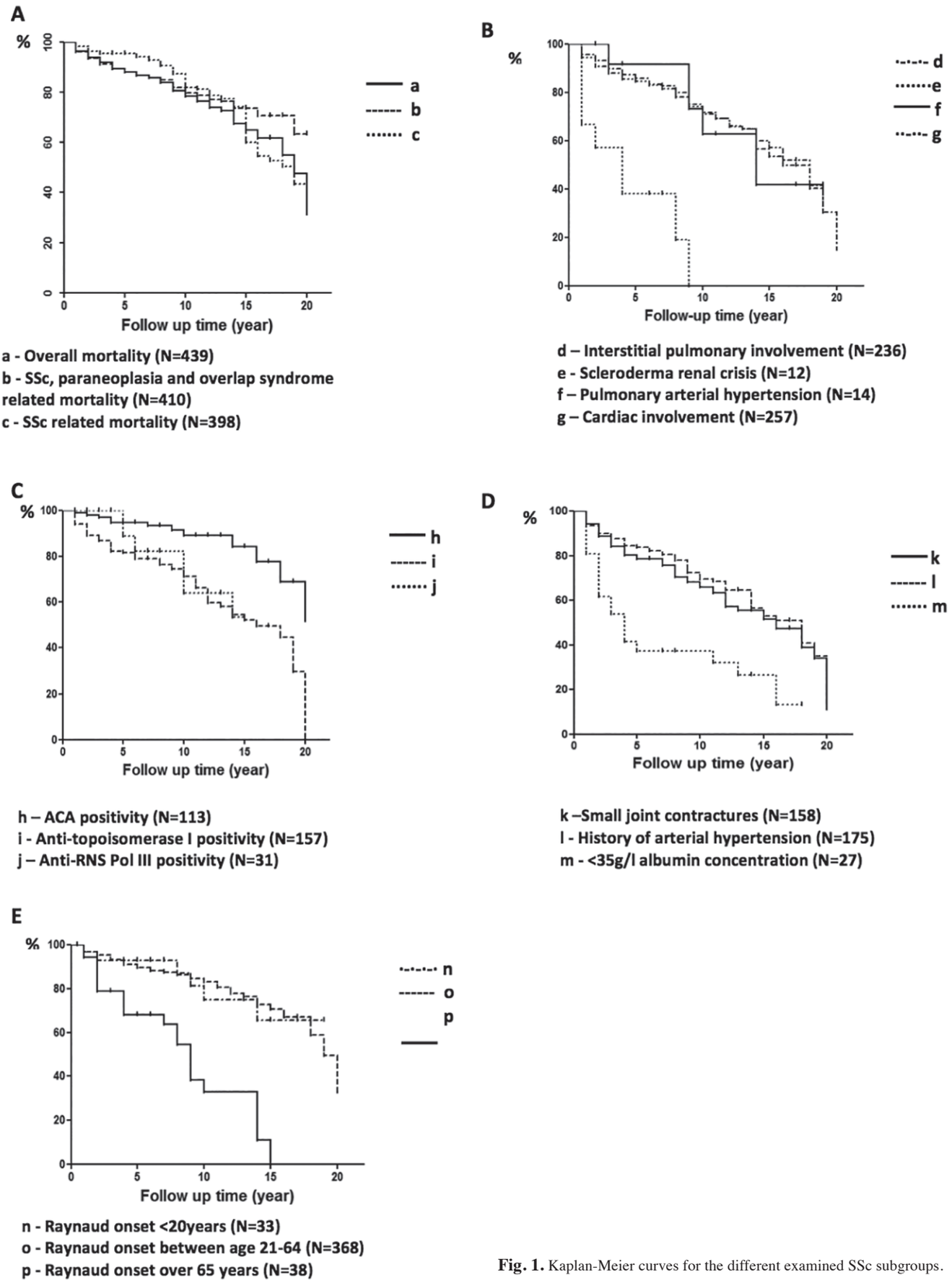

Fig. 1. Kaplan-Meier curves for the different examined SSc subgroups.

Table II. Multivariate analysis of 439 patients with SSc.

	Mortality risk for patients died of SSc related causes of death (excluding paraneoplasia and overlap syndromes)		Mortality risk for patients died of SSc related causes of death, paraneoplasia and overlap syndromes		Overall mortality risk	
(n.)	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Male gender (73)	3.877 (1.929-7.793)	<0.01	3.421 (1.858-6.301)	<0.001	3.256 1.883-5.631)	<0.001
Anti-topoisomerase I positivity (157)	1.730 (1.014-2.951)	<0.05	1.667 (1.023-2.714)	<0.05	2.158 (1.425-3.268)	<0.001
Small joint contractures ˜ (158)	2.758 (1.573-4.836)	<0.001	2.834 (1.721-4.665)	<0.001	1.834 (1.219-2.757)	<0.05
<70% FVC(72)					1.995 (1.146-3.470	<0.01
< 70% DLCO(216)					1.975 (1.281-3.045)	<0.01
< 50% DLCO(54)	2.680 (1.369-5.244)	<0.01	2.732 (1.597-4.673)			
> 40 mmHg right ventricular pressure on echocardiography (34)	4.974 (2.161-11.449)	<0.001	3.257 (1.515 -7.002)	<0.001	2.164 (1.219-3.842)	<0.01
< 50% ejection fraction (9)	4.468 (1.671-11.948)	<0.01	5.303 (2.065-13.618)	<0.01		
Brady ᶻ- or tachycardia ᶻᶻ detected by ECG (81)	2.321 (1.262-4.268)	<0.01	3.738 (2.207-6.332)	<0.001	2.514 (1.577-4.007)	<0.001
Arrhythmia on ECG (39)	1.973 (1.048-3.715)	<0.05			1.675 (1.022-2.746)	<0.05
Arterial hypertension* (175)	2.065 (1.220-3.495)	<0.01	2.063 (1.261-3.375)	<0.01	2.090 (1.390-3.143)	<0.01
Low haematocrit level (<33%) (45)	3.704 (2.046-6.704)	<0.01	2.728 (1.560-4.770)	<0.001	2.784 (1.749-4.430)	<0.01
Hypoalbuminaemia (<35g/l) (27)	2.481(1.255-4.904)	<0.001	2.769 (1.428-5.370)	<0.01	2.299 (1.283-4.119)	<0.01
Concurrent or history of malignancies (54)			3.190 (1.792-5.679)	<0.001	2.956 (1.835-4.762)	<0.001

*Systemic arterial hypertension was recorded if hypertension was diagnosed previously or diagnosis of hypertension was established simultaneously with SSc. ᶻ; ᶻᶻBrady- or tachycardia -consequently less than 60/min or higher than 85/min confirmed by a cardiologist it is heart manifestation related.
˜Small joint contractures were recorded if range of motion was less than 75% of normal in the metacarpophalangeal and proximal interphalangeal joints.

ence of anti-centromere antibodies and lack of giant capillaries, microhaemorrhages neoangiogenesis or avascularity showed a favourable outcome. In patients deceased of overlap syndrome and/or coexistent malignancy added to strictly SSc-related causes of death the same parameters made influence on survival by univariate analysis except for coexistent and previously diagnosed malignancies. (Fig. 1B, 1C, 1D)
Multivariate Cox analysis showed that male gender, presence of topoisomerase I antibody, DLCO and FVC<70%, presence of small joint contractures, more than 40 mmHg right ventricular pressure on echocardiography, ECG abnormalities, history of arterial hypertension, low haematocrit and albumin levels and presence of malignancies predict poor outcome.
Cox analysis, performed with exclusion patients died of SSc unrelated causes of death showed similar pattern, but arrhythmias, decreased FVC were no more independent predictors of mortality, while less than 50% of ejection fraction predicted worse outcome. Further exclusion of patients who died of paraneoplasia and overlap syndromes showed on multivariate analysis that abovementioned parameters with exception of malignancies and <70% DLCO and FVC predicted poor outcome (Table II).

Cause of death
During the follow-up 106 patients died, 77 (72.6%) because of SSc. In ten SSc related cases it was impossible to make distinction between different organ systems, multiple causes of death were declared. Sixteen patients' death was attributed to cardiac involvement, 8 to PAH, 13 to ILD, 2 to scleroderma renal crisis, 6 to gastrointestinal involvement and 5 treatment-related infections. In two cases kidney and ILD, in two cases kidney and gastrointestinal involvement, and in two cases ILD and infection were the causes of death. In one particular case infection and PAH, in 1 cardiac involvement and ILD, in 1 gastrointestinal involvement and infection, in 1 cardiac involvement and infection caused the death of the patients.
Out of the 17 cases of death due malignancies 12 patients died of coexistent malignancy (onset of the tumour ±5 years) and 5 because of other tumours, but connection between the onset of malignancy and SSc was clear, mainly due to therapy used for SSc.

Comparison of early and late onset SSc
33 patients were followed up fitting our early onset SSc criteria. The mean age at onset of Raynaud's syndrome (RP) was 15.2±4.3 years.
Patients having early onset SSc had a significantly more impaired FVC (<80%, 70% and 50%), conduction disturbances detected by ECG, and low BMI compared to cases with a disease onset between 21 and 64 years. Furthermore, significantly less early onset group patients had a history of PAH, malignancy and BMI>25 (Table III). In this particular subgroup, 6 (18.2%) out of the 33 patient died during the follow-up, four of them had dcSSc. Kaplan-Meier analysis revealed that poor survival was associated with the presence of FVC<70% and DLCO<70%, renal involvement, elevated ESR, decreased haemoglobin and haematocrit levels.
Out of the 439 examined patients 38 developed RP after the age of 65. The mean age at onset of RP was 69.9±3.9 years. When comparing clinical features of patients having late onset SSc we found significantly more patients having cardiac involvement, elevated right ventricular pressure on echocardiography, ECG disturbances and elevated ESR compared to patients with RP developed between age 21 and 64. On contrary, normal BMI was less frequent compared to patients with

Table III. Comparison of clinical features of patients with early and late onset SSc.

	Patients first RP[a] symptom started before age 20 n=33 (%)	Patients first RP[a] symptom started between age 21-64 n=368 (%)	Patients first RP[a] symptom started after age 65 n=38 (%)	RP[a] onset >65 years *vs*. onset 21-64 years *p* (Fisher exact test)	RP[a] onset <20 years *vs*. onset 21-64 years *p* (Fisher exact test
Male	8 (24.2)	57 (15.5)	8 (21.1)	NS[b]	NS
dcSSc	15 (45.4)	150 (40.8)	14 (36.9)	NS	NS
ACA positivity	5 (15.2)	95 (25.8)	13 (34.2)	NS	NS
Anti-topoisomerase positivity	13 (39.4)	127 (34.5)	17 (44.7)	NS	NS
Anti RNA Pol III positivity	2/11 (18.2)	28/119 (23.5)	1/5 (20)	NS	NS
Extensive pulmonary interstitial involvement[†]	8 (24.2)	84 (22.8)	11 (29)	NS	NS
Pulmonary interstitial involvement[††]	14 (42.4)	202 (54.9)	20 (52.6)	NS	NS
FVC<80%	12 (36.4)	58 (15.7)	2 (5.3)	NS	**<0.01**
FVC<70%	8 (24.2)	22 (6)	1 (2.6)	NS	**<0.001**
FVC<50%	3 (9.1)	5 (1.4)	0 (0)	NS	**<0.01**
Cardiac involvement[#]	21 (63.6)	203	33 (86.8)	**<0.0001**	NS
More than 40 mmHg right ventricular pressure on echocardiography	3 (9.1)	24 (6.5)	7 (18.4)	**<0.05**	NS
Conduction disturbance on ECG	9 (27.3)	52 (14.1)	6 (15.8)	NS	**<0.05**
Arrhythmia on ECG	2 (6.1)	29 (7.9)	8 (21.1)	**<0.05**	NS
History of arterial hypertension*	5 (15.2)	150 (40.1)	20 (52.6)	NS	**<0.01**
Scleroderma renal crisis^	1 (3)	11 (3)	0 (0)	NS	NS
Oesophageal involvement[§]	18 (54.6)	160 (43.5)	17 (44.7)	NS	NS
BMI <18	8 (24.2)	14 (3.8)	1 (2.6)	NS	**<0.001**
BMI 18-25	21 (63.6)	163 (44.3)	1 (2.6)	**<0.0001**	**<0.05**
BMI >25	4 (12.1)	181 (46.9)	16 (42.1)	NS	**<0.001**
Elevated ESR (>30mm/h)	8 (24.2)	100 (27.2)	19 (50)	**<0.01**	NS
Low haematocrit level (<33%)	4 (12.1)	36 (9.8)	5 (13.2)	NS	NS
Hypalbuminaemia (<35g/l)	0 (0)	23 (6.3)	4 (10.5)	NS	NS
Concurrent or history of malignancies	0 (0)	46 (12.5)	8 (21.1)	NS	**<0.05**
Coexistent malignancies	0 (0)	31 (8.42)	5 (16.1)	NS	NS

[a]RP: Raynaud phenomenon.
[b]NS: not significant.
[††]Pulmonary interstitial involvement (ILD) was recorded in case of fibrosis detected by high resolution computer tomography (HRCT) and concurrent decreased forced vital capacity (FVC <80%).
[†]Extensive pulmonary involvement was recorded in case of either the fibrosis affected the upper and middle area of the lungs on HRCT or FVC <50% or honeycombing was detected by HRCT.
[#]Cardiac involvement was recorded if the patient had at least one of the following ~~items~~: decreased ejection fraction <50%, elevated right ventricular pressure detected by echocardiography (>40 mmHg-except in patient with severe pulmonary involvement), relaxation disorder (defined by the cardiologist evaluation based on E/A ratio), abnormal electrocardiogram (ECG) (arrhythmia, conduction disturbances, brady- or tachycardia; heart rate consistently <60/min or higher than 85/min confirmed by cardiologist that it is heart manifestation related).
[§]Oesophageal involvement was recorded if patient had dysphagia and/or barium-swallowing x-ray showed dys/hypomotility and/or strictures/dilatation.
^Scleroderma renal crisis (SRC) (including the normotensive form) was defined by two experts (GK, LC) based on the definition: a new onset of significant systemic hypertension (>150/85 mmHg) and decreased renal function (≥30% reduction in estimated glomerular filtration). Normotensive cases were registered if there was no change in blood pressure but other manifestations of SRC occurred.
*Systemic arterial hypertension was recorded if hypertension was diagnosed previously or diagnosis of hypertension was established simultaneously with SSc.
**Coexistent malignancy was recorded in cases when time between malignancy and SSc onset was maximum 5 years.

RP developed between age 21 and 64 (p<0.0001) (Table III).

Twenty-one (55.3%) out of the 38 patients died before the end of the 2015. Poor prognosis was associated with decreased haemoglobin and albumin levels and elevated CRP.

In the early onset group, the 5, 10, 15 years survival rates were 93%, 75% and 66%, respectively. In the elderly onset group the 5 and 10 years survival rates were 66% and 32%, respectively. Patients with RP onset between age 21 and 64 had 91% 5 years survival rate, 84% 10 years survival rate and 72% 15 years survival rate. Survival was significantly worse in patients with Raynaud's onset after age 65 compared to the other two patients groups (p<0.001) (Fig. 1E).

Discussion

Our aim was to investigate the risk factors of mortality in a large series of patients followed up for a relatively long time period with low lost to follow-up rate. In our study the leading cause of death was the cardiopulmonary manifestation of the disease which is in accordance with international observations (5, 12, 14, 15, 20, 23, 24, 26, 28, 37, 38). An improvement of survival is observable in SSc, in 1971 Bennett found 50% 10 years survival rate (29), in 1991 Lee found 61% 10 year survival rate (6), and in the last decade the 10 year survival rate varied between 64–88% (2, 12, 14, 15, 17, 23, 25, 26, 28). The survival rate we found was similar to those published in recent studies, and it was also better than previous decades (Table IV). The survival improved compared to our previous survival analysis (22); in the abovementioned study the 10 years survival rate was 72.6% compared to 79.9% in the present study. This is possible due to shorter time between disease onset

Table IV. Demographic data and mortality rates reported in different large systemic sclerosis cohorts from 1971 to 2015*.

First author	Year of publication	Patient enrolment	Country	n. of patients	Deceased patients %	Male %	dcSSc %	Age at onset	Age at diagnosis	Disease duration	Follow-up time	5-year survival %	10-year survival %	15-year survival %	20-year survival %
Bennett *et al*. (29)	1971	1947-1970	English	67	38.8	16.4	NA	NA	46.2	NA	NA	73	50	NA	NA
Farmer *et al*. (32)	1960	1945-1952	English	271	48.7	26.6	NA	NA	42.9	NA	103.8m	NA	NA	NA	NA
Lee *et al*. (6)	1991	1979-1990	Canadian	237	25.7	17.3	43	NA	43.3	3.8y	5.7y	3 year: 86%//6 year: 76%//9 year: 61%			
Altman *et al*. (27)	1991	1983-1985	American	264	50	NA	NA	NA	NA	NA	5.2y	2 year: 80% 12 year 30%			
Czirják *et al*. (9)	1993	1982-1992	Hungarian	118	22,8	10.2	28	NA	NA	NA	5.8y	NA	NA	NA	NA
Hesselstrand *et al*. (24)	1998	1983-1995	Swedish	249	49	45	25	44.9	NA	10.4 y	5.8 y	86	69	NA	NA
Jacobsen *et al*. (8)	1998	1960-1996	Danish	344	46.51	19	34	NA	55	8.6 y	NA	81	71	55	42
Bryan *et al*. (11)	1999	1982-1991	English	280	27.14	23.2	47.4	45.7	NA	17 m	NA	NA	NA	NA	NA
Geirsson *et al*. (5)	2001	1982-1995	Swedish	100	30	33	34	42.4	NA	NA	7.7y	NA	NA	NA	NA
Ferri *et al*. (15)	2002	1955-1999	Italian	1012	27.6	11.36	44	NA	NA	NA	7.1y	NA	69.2	NA	45.5
Scussel-Lonzetti *et al*. (13)	2002	1984-1999	Canadian	309	21.3	14.3	9.4	NA	NA	NA	NA	NA	NA	NA	NA
Simeon *et al*. (17)	2003	1976-1996	Spanish	79	15.2	14.	28	44.2	48.8	4.5	NA	71	64	62	NA
Mayes *et al*. (16)	2003	1989-1998	American	706		16.3			46.1			77.9	55.1	37.4	26.8
Ionnadis *et al*. (18)	2005	NA	NA	1645	35.1	19.8	44.6		49.6		7y	NA	NA	NA	NA
Trad *et al*. (13)	2005	1980-2004	French	86	19.7	13.6	100		44.5		72.5m				
Czirják *et al*. (22)	2007	1983-2005	Hungarian	366	25.41	13.9	27.6	NA	NA	13.5 y	6y	84	72.6	NA	NA
Arias Nunez *et al*. (49)	2008	1998-2006	Spanish	78	25.6	21.5	29.5	51.6	59.8	NA	6.6y	83.9	64.9	57.6	NA
Assasi *et al*. (31)	2009	2005-2008	American	250	14.9	16	57.4	48.8	NA	NA	6.2y	NA	NA	NA	NA
Hachulla *et al*. (4)	2009	2002-2003	French	546	8.6	15.9	27.5	46	47.8	NA	3.1y	NA	NA	NA	NA
Joven *et al*. (14)	2010	1980-2006	Spanish	204	NA	11	31	43	49	NA	8y	85	75	NA	55
Kim *et al*. (2)	2010	1972-2007	Korean	230	14.3	10.9	43.9	NA	43.7	NA	8.6y	85.4	80.1	NA	NA
Tyndall *et al*. (20)	2010	2004-2008	European	5860	5.2	19.4	35.6	NA	NA	NA	0.9y	NA	NA	NA	NA
Al-Dhaher *et al*. (28)	2010	1994-2004	Canadian	185	23	NA	37	NA	NA	9.1	NA	90	82	NA	NA
Hissaria *et al*. (10)	2011	1993-2007	Australian	736	42.11	19.9	19.3	46.7	NA	16,4y	NA	74	NA	NA	NA
Hashimoto *et al*. (25)	2011	1973-2008	Japanese	405	21.2	7.2	32.6	47	NA	14y	NA	NA	88	NA	77.4
Sampio-Barros *et al*. (26)	2012	1991-2010	Brazil	947	17.7	11.5	31	42.6	NA	12.6y	9.6y	90	84	NA	NA
Hoffmann *et al*. (23)	2013	1999-2009	Norwegian	312	14	NA	NA	47	54	9.9y	8.1y	95	86	NA	NA
Ferri *et al*. (12)	2014	2000-2011	Italian	821	9.1	9.1	12.5	53.7	NA	3.6y	4.5y	NA	80.7	NA	NA
Alba *et al*. (19)	2014	2006-2012	Spanish	1037	14.6	12	40	45	51	NA	5.2y	90.7	NA	NA	NA
Simeón-Aznar *et al*. (1)	2015	1970-2008	Spanish	879	15.7	14.8	27.6	NA	NA	NA	N	96	93	NA	83

*Studies on SSc patients recruiting basic information on organ manifestation were selected. Studies investigating one specific organ involvement, subset or race were excluded (53).

Table V. Risk ratio of different factors affecting survival in series of scleroderma by multivariate analysis*.

First author	Male sex	dcSSc	PAH	Lung	Heart	Kidney	Low BMI	Anti Scl70	Hyper-tension	Osteo-articular / joint involvemnt	Cancer	Age at onset	Low haemo-globin level	Elev-ated ESR	Elev-ated right ventri-cular preasure	higher mRSS	Protein-uria	Digital ulcer
Lee *et al*. (6)	1.1			2.3	5	2.8						1.2						
Ferri *et al*. (15)	1	5.27		2.52		8.1						1.08						
Scussel-Lonzetti *et al*. (3)				4.3								1.036	2.37	3.89				
Trad *et al*. (13)			4.09			4.10						1.057						
Czirják *et al*. (22)	1.13	2.37		3.38							3.2			3				
Hachulla *et al*. (4)			7.246									1.052						
Assasi *et al*. (31)				2.46			12.94		3.14			4.37						
Altman*et al*. (27)	1.47																	
Kim *et al*. (2)		2.5		2.8	4.2			3				1.7-7.4						
Tyndall *et al*. (20)			2.018	1.644								1.295				1.198	3.343	
Ioannidis *et al*. (18)	1.5			1.6	2.8	1.9		1.3				1.6						
Joven *et al*. (14)			2.2	2		4.5						1.2						
Hasimoto *et al*. (25				2.21	1.77	1.35												
Sampaio-Barros *et al*. (26)	2,35			4.2		9.96				4.38						1.71		
Clements *et al*. (7)				6.09												3.69		
Hoffmann *et al*. (23)	2.1	2.8	8	3.1														
Alba *et al*. (19)		2.22	1.89	1.79		6.16						1.05						
Frasen *et al*. (21)												1.03		1.89			2.29	
Bryan *et al*. (11)														7.4			23.6	
Ferri *et al*. (12)	6.05			5.34		10.49						1.03			4.98			2.78
Simeón-Aznar (1)	1.115	2.700	2.69		3.187	6.448												

*The publications using multivariate regression analysis were selected.

and enrolment or better therapeutic options.

Our results are in accordance with previous univariate analysis, we have also confirmed that dcSSc (4, 5, 9-12, 14, 15, 20, 22-26, 28) male gender (4, 8, 10, 15, 16, 20, 22-26), pulmonary (6, 7, 9, 10, 12, 14-16, 22, 23, 25) and cardiac involvement (2, 6, 7, 9, 12, 15, 22, 25, 28, 32), scleroderma renal crisis (6-10, 12, 15-17, 20, 22, 25, 32), elevated right ventricular pressure (12, 20), decreased ejection fraction (20), ECG abnormalities (3, 11, 29), decreased DLCO (3, 4, 7, 11, 20) and FVC (2, 4, 5, 7, 17, 20, 22, 27), oesophageal involvement (9, 27) were associated with poor survival. Furthermore, anti-topoisomerase I antibody positivity (3, 12, 20, 22), scleroderma capillary pattern (10, 17), anaemia (3, 7, 9, 22, 27, 32), elevated ESR (3, 7, 9, 12, 14, 22, 32) were poor prognostic signs. Conversely anti-centromere antibody was associated with favourable outcome (9, 22, 23, 25). We also confirmed, as in former studies, that low concentration of haemoglobin and/or low haematocrit (22, 3, 7, 27) independently predict poor outcome. Most of the factors predicting poor outcome are indexed in different activity indeces, hence higher activity may predict poor outcome (39).

Our study showed that lower than 35g/l concentration of serum albumin level was also associated with increased mortality risk, confirming previous findings, also showing data that low albumin level was significantly frequently present among deceased patients (27) (Table V). Most of the findings of our previous survival analysis studies (7, 22) were confirmed except the presence of skin pigmentation abnormalities which was not associated with poor survival in our current investigation. The time between disease onset and patients enrolment was shorter which may partially explain this particular difference between the current and earlier studies.

The presence of osteoarticular involvement - definition not added - was a risk factor of mortality in a large series of patients from Brazil (26). Joint deformity was also significantly more frequently present among deceased patients in a univariate analysis in an American cohort (27). Presence of contractures was associated with increased mortality risk in another series as well (7). An earlier Hungarian study on a cohort independent from this particular study already indicated that presence of hand deformity with contractures is associated with a poor survival (9). Our new study demonstrated that presence of small joint contractures is an independent poor prognostic marker of mortality in patients with SSc.

Univariate analysis of the EUSTAR database showed that patients with arterial hypertension had significantly worse outcome (HR=1.38, $p<0.007$) (20). This was also confirmed in Canadian and American studies as well (28, 31). In our series the presence of history of hypertension was strongly associated with mortality, the risk of mortality was twice compared to patients with no arterial hypertension.

It is well-known that patients with SSc have a higher risk for malignancies compared to the general population. Some studies revealed a close temporal relationship between onset of SSc and tumours (40), especially in patients with anti-polymerase III antibodies (40). It is supposed that genetic susceptibility, like mutations of POLR3A gene can result in both SSc and cancer development (41). Patients with anti-polymerase III and diffuse subtype were at higher risk for short SSc-cancer interval (40), but in accordance with our current study, malignancy can develop in other subsets including patients with lcSSc (40). Sixty percent of patients with coexistent malignancies had lcSSc. In our series only 2 (5%) patients were anti-RNA-polymerase III positive and more than 20 (55.5%) ACA or topoisomerase positive. Similarly to other series (40), we did not find any significant differences in the clinical features of patients with and without coexistent malignancies.

Other studies revealed that presence of coexistent malignancies influence the survival (10, 14, 22), however not all of these particular studies made distinctions between early and/or late onset malignancies. In a Spanish study the most common types of neoplasia were breast cancer- similar to our study and skin cancer (14), but clear distinction between paraneoplastic and non-paraneoplastic cases was not made. Our previous Hungarian study examining patients of two tertiary care centers (Pécs, Debrecen), proved in a multiple regression analysis that presence of early malignancies were associated with additional risk (22). In this particular study we demonstrated the increased risk for survival only by univariate analysis, probably due to the recent better diagnostic and therapeutic possibilities available.

Onset of the disease is usually in the forties of the patients (2, 4, 5, 14, 17, 24, 31), but SSc can develop in younger (19, 42-47) and elderly patients (19, 48-51) too. In the EUSTAR database 1.2% of cases accounted to early onset SSc (47). Prognostic factors of the childhood disease are rarely investigated because of low incidence, but previous studies showed pericarditis (44), heart failure (44), arrhythmias (44) were associated with poor survival. A multicenter study investigating the juvenile SSc revealed that gastrointestinal, pulmonary, cardiovascular, central nervous system and renal involvement were frequent among deceased patients (45). Follow-up investigations of SSc starting in young ages or elderly patients are rarely published, mainly due to a low incidence. In previous studies the upper limit of early SSc varied between 16 to 30 years (19, 40, 44, 47). Based on our results we can confirm the already known fact that renal involvement (45) is associated with poor outcome in the early onset form too. Furthermore, opposed to Martini's (44) work we found that decreased FVC as well as low haemoglobin and haematocrit concentrations are associated with poor survival similarly to the adulthood disease. In the early onset SSc subgroup we found significantly more patients with decreased FVC, low body weight and conduction disturbances at enrolment compared to the "middle aged" group (onset of 21-64 years). Conduction disturbances were also more frequently present in this particular young age group in a Spanish series of patients, but it did not reach the statistically significant level (19).

Late onset scleroderma is a rarely studied form of the disease too, previously 1.4-19% of prevalence was reported (19, 48, 50-52). Survival in elderly patients is significantly lower compared to patients with not elderly onset SSc patients (51). Generally lcSSc is more frequent in this population (19, 50-52), but in our previous series of SSc diffuse subset was more frequent (48). Patients with elderly onset SSc patients have a higher risk for pulmonary hypertension (51-52), cardiac disease (50-52), pulmonary (48, 49, 51) and renal (50) involvement compared to patients with younger-age at disease onset. The definition of late onset SSc varies between wide ranges, 60–75 year was the cut off value previously (19, 48-52). The late onset form seems to be a milder type of the disease; the limited form was more common among these patients as in other studies (19, 49-52). The higher prevalence of cardiac involvement in elderly patients might be explained by the high incidence of cardiac disease in the general elderly population. Significantly higher rate of cardiac involvement (including ECG abnormalities) was also presented in other studies (19, 50-52), hence we can claim our patients having late onset SSc are quite similar to patients in other regions.

Our study has some limitations. We cannot rule out the referral bias, it is highly possible that patients with milder SSc were less frequently referred to our center. The strength of our study is that the proportion of cases lost to follow-up is low.

In conclusion this is the first time to our knowledge when the presence of small joint contractures and hypoalbuminaemia were presented as independent prognostic factors of the disease. We confirmed the previous findings that the internal organ involvements in SSc are associated with a higher mortality risk. Patients with history of arterial hypertension have a higher risk for mortality.

The early and late onset forms of the disease are a bit different when compared to the average spectrum of the disease; patients developing SSc in early life are prone to have decreased spirometry functions.

Coexistent malignancies exist both in dcSSc and lcSSc, therefore the possible presence of a coexistent malignancy at disease onset may be considered not only in patients with RNA-polymerase III antibodies but in other subsets of patients as well.

Key messages

- Presence of small joint contractures at onset of SSc is associated with higher mortality risk.
- Patients with history of systemic arterial hypertension are at higher risk for mortality.
- Patients with Raynaud syndrome onset before age 20 are likely to have a decreased FVC.

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