Chapter 3

Survival, Mortality, Causes of Death and Risk Factors of Poor Outcome

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Additional information is available at the end of the chapter

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Abstract

Systemic sclerosis is a rare autoimmune disorder with a historically bad prognosis. Survival has been improving over time and we can currently estimate a 1-year survival, 94.9; a 5-year survival, 84.4; a 10-year survival, 70.9 and a 20-year survival, 44.9%, from the time of diagnosis. Accordingly, mortality has been decreasing over time, being the overall standardized mortality ratio (SMR) 2.72 (1.90–3.83), SMR 2.4 after 1990. Among the SSc-related causes of death, the lung death is the most important cause and its relative percentage is increasing over time since the introduction of ACE inhibitors for the treatment of scleroderma renal crisis (SRC) in early 1990s. Among the SSc-non-related causes of death, cancer, infection and cardiovascular disorders are the leading causes of death. Risk factor predictors of poor outcomes are an elder age at diagnosis, the male gender, diffuse subset, visceral involvement and non-Raynaud's phenomenon onset.

Keywords: systemic sclerosis, survival, mortality, death, prognosis

1. Introduction

Systemic sclerosis (SSc) represents one of the autoimmune systemic diseases with worse prognosis. It was actually a devastating scenario until it became well advanced in the twentieth century in terms of survival and mortality, but since late 1980s, the knowledge and course of scleroderma have been progressively improving. Nowadays, more risk factors are recognized and allow physicians to focus on patients with worse prognosis. As traditional SSc-related involvements improved, secondary involvements or SSc-non-related diseases have gained prominence.

2. Survival

Scleroderma was a devastating disease for ages. Physicians were short of proper tools to change significantly the prognosis of the disease since late 1980s–early 1990s due to the introduction of new therapies, firstly angiotensin converting enzyme (ACE) inhibitors for the treatment of the scleroderma renal crisis (SRC) and, in late 1990s-early 2000s, due to the implementation of pulmonary arterial hypertension (PAH) treatment with new drugs such as phosphodiesterase five (PDE5) inhibitors and antagonists of the receptor of endothelin (AREs). Survival has improved over time, measured at any time of the follow-up, from onset (in most studies described in the form of Raynaud's phenomenon) as well as from diagnosis and what is more important is that it keeps improving. This is true that survival in all stages has improved but especially 1-year and 5-year survival. Since late death is related the most to SSc-non-related causes, it might be reflecting the fact that physicians are improving significantly the prognosis of SSc-related involvements but not that much in other SSc-non-related diseases. Thus, just like in other autoimmune diseases, scleroderma is becoming step-by-step a chronic disease and not a terminal and deleterious diagnosis.

Prior to the assessment of survival of any cohort, we must pay attention to the methodology of the study because there is a huge variability among them, sometimes assessing survival from diagnosis and sometimes from the onset of disease. These last data are obviously a more imprecise data but certainly more real. Several survival and mortality studies from single cohorts and reviews have been published from the last mid-century, reporting data about cumulative survival at different times of follow-up and measured sometimes from the onset of disease and sometimes from the time of diagnosis (**Table 1**) [1–42].

We show data previously released in Seminars in Arthritis and Rheumatism in the last and more precise meta-analysis, so that we can currently predict at the time of diagnosis: a 1-year survival, 94.9; a 5-year survival, 84.4; a 10-year survival, 70.9 and a 20-year survival, 44.9% (**Table 2** and **Figure 1**) [43].

Study	Country	Years (mid-cohort)	1-year survival	5-year survival	10-year survival	20-year survival	From onset/diagnosis
Tuffanelli [1]	The USA	1935–1958(46)	NA	70.3%	69%	NA	Diagnosis
Farmer [2]	The USA	1945–1952(48)	NA	53%	NA	NA	Diagnosis
Bennet [3]	The UK	1947–1970(58)	94%	73%	50%	NA	Diagnosis
Medsger [4]	The USA	1955–1970(62)	78%	48%	NA	NA	Diagnosis
Zarafonetis [5]	The USA	1948–1980(64)	NA	81.4%	69.4%	NA	Diagnosis
Medsger [6]	The USA	1963–1970(66)	70%	44%	NA	NA	Diagnosis
Rowell [7]	The UK	1960–1975(67)	NA	NA	74%	NA	Onset (first Raynaud)
Barnett [8]	AUS	1953–1983(68)	NA	83.6%	59.3%	27.1%	Onset (first Raynaud)
Gouet [9]	FR	1960–1984(72)	88%	62.5%	50.5%	NA	Diagnosis

Study	Country	Years (mid-cohort)	1-year survival	5-year survival	10-year survival	20-year survival	From onset/ diagnosis
Giordano [10]	ITA	1965–1983(74)	NA	72%	32%	NA	Diagnosis
Altman [11]	The USA	1973–1977(75)	NA	63%	42%	NA	Diagnosis
Eason [12]	NZ	1970–1980(75)	85%	60%	42%	NA	Diagnosis
Wynn [13]	The USA	1970–1980(75)	98.4%	68.9%	51.2%	31.7%	Diagnosis
Peters-Golden [14]	The USA	1972–1983(77)	84%	66%	60%	NA	Diagnosis
Ferri [15]	ITA	1955–1999(77)	NA	83%	69.2%	45.5%	Diagnosis
Lally [16]	The USA	1972–1984(78)	NA	77%	NA	NA	Diagnosis
Jacobsen [17]	DEN	1960–1996(78)	NA	81%	71%	42%	Onset (first non-Raynaud's symptom)
Kuwana [18]	JAP	1971–1990(80)	NA	NA	NA	NA	Diagnosis
Geirsson [19]	ICE	1975–1990(82)	NA	100%	81%	NA	Diagnosis
Kaburaki [20]	JAP	1976–1991(83)	NA	78%	68.2%	NA	Diagnosis
Nishioka [21]	JAP	1974–1994(84)	NA	93.7%	82%	56.7%	Onset (first Raynaud)
Simeón [22]	SPA	1976–1996(86)	NA	71%	64%	62%	Onset (first Raynaud)
Bulpitt [23]	The USA	1982–1992(87)	92%	68%	NA	NA	Onset (first non-Raynaud's symptom)
Bryan [24]	The UK	1982–1992(87)	NA	87%	75%	NA	Onset (first non-Raynaud's symptom)
Nagy [25]	HUN	1982–1993(87)	NA	82.9%	70.4%	NA	Onset (first non-Raynaud's symptom)
Hesselstrand [26]	SWE	1983–1995(89)	NA	92%	78%	NA	Onset (first non-Raynaud's symptom)
			NA	86%	69%	NA	Diagnosis
Kim [27]	KOR	1972–2007(89)	NA	85.4%	80.1%	NA	Diagnosis
Mayes [28]	The USA	1989–1991(90)	NA	77.9%	55.1%	26.8%	Diagnosis
Hashimoto [29]	JAP	1973–2008(90)	NA	NA	88%	77.4%	Onset (first Raynaud)
Pérez-Bocanegra [30]	SPA	1976–2007(91)	NA	89%	81%	63%	Diagnosis
Alamanos [31]	GRE	1981–2002(91)	NA	83%	70%	NA	Diagnosis

Study	Country	Years (mid-cohort)	1-year survival	5-year survival	10-year survival	20-year survival	From onset/ diagnosis
Nihtyanova [32]	The UK	1990–1993(91)	NA	84.2%	NA	NA	Diagnosis
		2000–2003(01)	NA	89.9%	NA	NA	Onset (first non-Raynaud's symptom)
Joven [33]	SPA	1980–2006(93)	95%	85%	75%	55%	Onset (first non-Raynaud's symptom)
Ruangjutipopan [34]	THAI	1987–2001(94)	NA	73%	67.4%	NA	Onset (no definition)
Czirják [35]	HUN	1983–2005(94)	NA	84%	72.6%	NA	Diagnosis
Arias-Núñez [36]	SPA	1988–2006(97)	NA	83.9%	64.9%	NA	Diagnosis
Alba [37]	SPA	1986–2010(98)	NA	90.7%	NA	NA	Diagnosis
Al-Dhaher [38]	CAN	1994–2004(99)	NA	90%	82%	NA	Diagnosis
Sampaio-Barros [39]	BRA	1991–2010(00)	NA	90%	84%	NA	Onset (no definition)
Hoffmann-Vold [40]	NOR	1999–2009(04)	NA	95%	86%	NA	Onset (first non-Raynaud's symptom)
Vettori [41]	ITA	2000–2008(04)	NA	94.8	NA	NA	Onset (first Raynaud)
Kuo [42]	TAIW	2002–2007(05)	94.9%	83.2%	NA	NA	Diagnosis

NA: non-available. Reprinted from Rubio-Rivas et al. [43], with permission from Elsevier.

Table 1. Survival studies on scleroderma [43].

	Survival from onset (first Raynaud)			Survival from onset (first non-Raynaud's symptom)			Survival from diagnosis		
	Before 1990 (five studies)	After 1990 (three studies)	p	Before 1990 (four studies)	After 1990 (three studies)	p	Before 1990 (18 studies)	After 1990 (eight studies)	p
Number of patients	840	1693		846	802		4365	3476	
1-year survival% mean (SD)	–	–	–	92 (NA)	95 (NA)	–	85.3(9.5)	94.9(NA)	0.384
5-year survival% mean (SD)	85.1(10.4)	92.8(2.9)	0.385	79.7 (8.2)	90 (5.0)	0.118	70.6(14.3)	84.4(3.8)	0.001
10-year survival% mean (SD)	71.5(9.5)	88(NA)	0.189	72.1 (2.5)	80.5 (7.8)	0.358	58.8(14.8)	70.9(10.1)	0.086

	Survival from onset (first Raynaud)			Survival from onset (first non-Raynaud's symptom)			Survival from diagnosis		
	Before 1990 (five studies)	After 1990 (three studies)	p	Before 1990 (four studies)	After 1990 (three studies)	p	Before 1990 (18 studies)	After 1990 (eight studies)	p
20-year survival% mean (SD)	48.6(18.8)	77.4(NA)	0.316	42 (NA)	55 (NA)	–	38.6(9.8)	44.9(25.6)	0.790

T-test for independent groups among studies before and after 1990 (mid-cohort year). NA: non-available. Reprinted from Rubio-Rivas et al. [43], with permission from Elsevier.

Table 2. Survival studies on scleroderma [43].

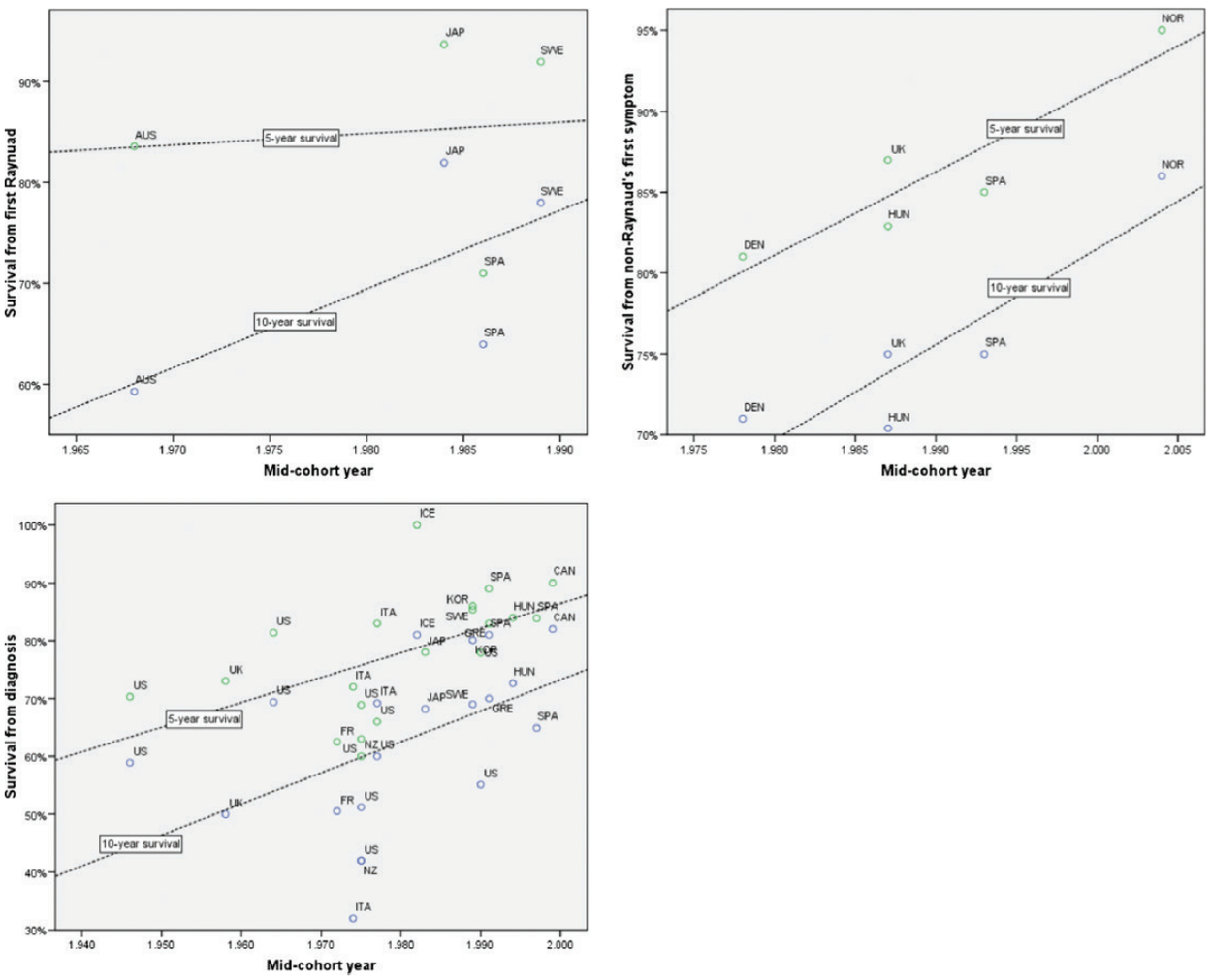

Figure 1. Survival evolution over time. Meta-regression. Five-year survival (coefficient b = 0.308 and p = 0.402) and 10-year survival (coefficient b = 0.595 and p = 0.237) from the onset (first Raynaud). Five-year survival (coefficient b = 0.612 and p = 0.113) and 10-year survival (coefficient b = 0.590 and p = 0.037) from the onset (first non-Raynaud's symptom). Five-year survival (coefficient b = 0.595 and p < 0.001) and 10-year survival (coefficient b = 0.536 and p = 0.025) from diagnosis. Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

3. Mortality

SSc is an autoimmune disease with a broad spectrum of severity, ranging from a mild disease to a devastating one. The most valuable parameter in order to compare mortality (instead of a crude mortality rate) is the assessment of the SMR, a fundamental tool in the only five mortality meta-analyses reported so far in SSc (**Table 3**). The SMR is the ratio between observed mortality and expected mortality in sex- and age-matched general population. These five meta-analyses are based on the assessment of the SMR: Elhai et al. {nine studies, overall SMR is 3.53 (3.03–4.11)} [45], Loannidis et al. {seven studies} [44], Toledano et al. {seven studies, overall SMR 3.51 (2.74–4.50)} [46], Komócsi et al. {10 studies, overall SMR 3.24} [47] and Rubio-Rivas et al. {17 studies, overall SMR 2.72 (1.90–3.83)} [43]. In base of this last study based on 17 studies, we could state that mortality is over 2.7-fold compared to the general population (**Table 4** and **Figure 2**) [5, 17, 24, 26, 29, 30, 31, 33, 37, 40, 42, 48–53]. Mortality has been decreasing over time and notoriously after 1990, being more reasonable to accept nowadays an SMR over 2.4-fold in a patient diagnosed today (**Figure 2**). Obviously, prognosis should be individualized since different risk factors present at diagnosis or during the follow-up can modify this predicted SMR. For instance, SMR in males and dcSSc subset is expected to be worse compared to SMR in females or lcSSc subset (**Figure 3**).

Study	Year of publication	Number of studies included	SMR (95% CI)
Ioannidis et al. [44]	2005	7	–
Elhai et al. [45]	2012	9	3.53 (3.03–4.11)
Toledano et al. [46]	2012	7	3.51 (2.74–4.50)
Komócsi et al. [47]	2012	10	3.24 (NA)
Rubio-Rivas et al. [43]	2014	17	2.72 (1.93–3.83)

NA: non-available.

Table 3. Meta-analyses on scleroderma and mortality.

Study	Country	Years (mid-cohort year)	Death	Overall SMR (95%CI)	dcSSc SMR (95%CI)	lcSSc SMR (95%CI)	Male SMR (95%CI)	Female SMR (95%CI)
Zarafonetis [5]	US	1948–1980 (64)	142	5.40 (3.17-7.63)	NA	NA	NA	NA
Jacobsen [17]	DEN	1960–1996 (78)	160	2.90 (2.50-3.40)	4.50 (3.50-5.70)	2.30 (1.80-2.80)	3.70 (2.70-5.10)	2.70 (2.30-3.30)
Abu-Shakra [48]	CAN	1976–1990 (83)	61	4.69 (3.73-5.65)	6.18 (4.17-8.81)	3.80 (2.58-5.39)	4.18 (2.09-7.48)	4.81 (3.65-6.44)
Walsh [49]	US	1981–1990 (85)	2123	1.05 (1.01-1.1)	NA	NA	NA	NA
Bryan [24]	UK	1982–1992 (87)	55	4.05 (3.03-5.22)	NA	NA	3.22 (1.85-4.97)	4.59 (3.22-6.19)
Hesselstrand [26]	SWE	1983–1995 (89)	49	4.59 (3.48-6.07)	6.06 (4.09-9.02)	3.72 (2.41-532)	4.77 (3.21-7.09)	4.44 (2.87-6.34)
Hashimoto [29]	JAP	1973–1908 (90)	86	2.76 (2.18-3.35)	5.90 (4.20-7.61)	1.71 (1.18-2.24)	3.31 (1.15-5.47)	2.71 (2.10-3.32)

Study	Country	Years (mid-cohort year)	Death	Overall SMR (95%CI)	dcSSc SMR (95%CI)	lcSSc SMR (95%CI)	Male SMR (95%CI)	Female SMR (95%CI)
Alamanos [31]	GRE	1981–2002 (91)	36	2.0 (1.2-2.8)	NA	NA	NA	NA
Scussel-Lonzetti [50]	CAN	1984–1999 (91)	66	2.69 (2.10-3.40)	6.17 (2.80-11.70)	2.71 (1.85-3.80)	1.76 (0.80-3.30)	2.55 (1.90-3.30)
Pérez-Bocanegra [30]	SPA	1976–2007 (91)	73	1.90 (1.50-2.30)	6.50 (4.10-9.80)	1.70 (1.20-2.20)	1.80 (0.80-3.40)	2.50 (1.90-3.20)
Joven [33]	SPA	1980–2006 (93)	44	3.10 (1.60-6.10)	NA	NA	NA	NA
Alba [37]	SPA	1986–2010 (98)	151	3.80 (3.18-4.43)	NA	NA	NA	NA
Hissaria [51]	AUS	1993–2007 (00)	331	1.46 (1.28-1.69)	2.92 (2.20-3.89)	1.30 (1.11-1.53)	NA	NA
Mok [52]	CHI	1999–2008 (03)	110	3.94 (3.20-4.68)	NA	NA	2.59 (1.32-3.87)	4.32 (3.45-5.20)
Hoffmann-Vold [40]	NOR	1999–2009 (04)	43	2.03 (1.40-2.60)	5.33 (3.90-10.30)	1.62 (1.10-2.50)	2.61 (1.40-3.90)	1.80 (1.20-2.70)
Strickland [53]	UK	1999–2010 (04)	53	1.34 (0.95-1.74)	1.66 (0.83-2.97)	1.27 (0.92-1.72)	1.54 (0.67-3.04)	1.30 (0.95-1.74)
Kuo [42]	TAIW	2002–2007 (05)	204	3.24 (2.82-3.71)	NA	NA	3.53 (2.97-4.16)	2.92 (2.29-3.66)

NA: non-available, SMR: standardized mortality ratio, dcSSc: diffuse cutaneous systemic sclerosis and lcSSc: limited cutaneous systemic sclerosis. Reprinted from Rubio-Rivas et al. [43], with permission from Elsevier.

Table 4. Studies included in the SMR meta-analysis by Rubio-Rivas et al [43].

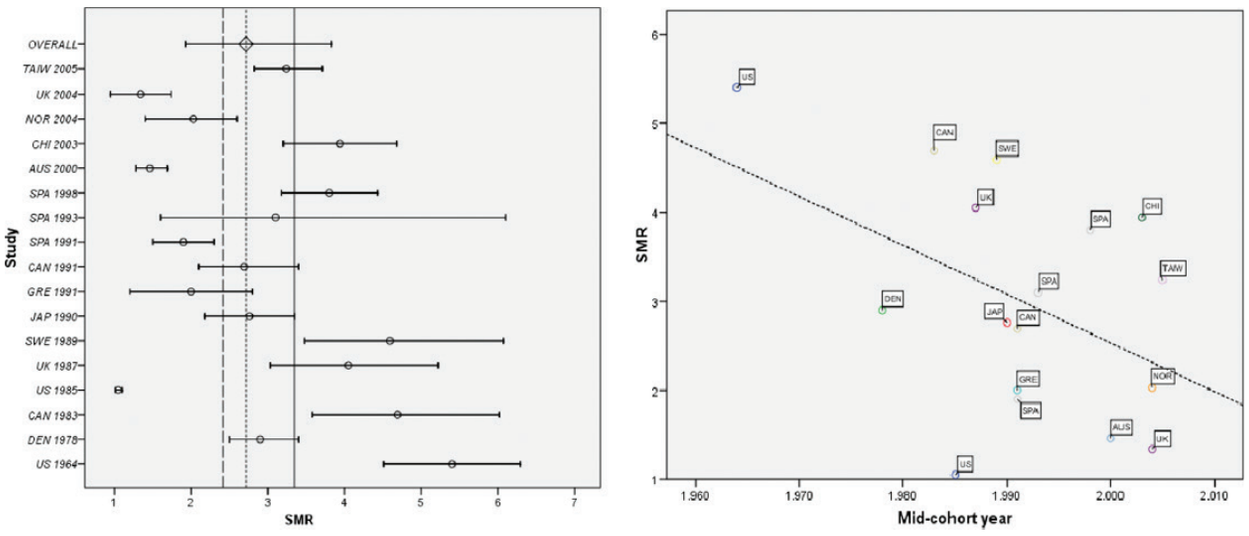

Figure 2. SMR meta-analysis. The overall SMR (discontinuous points) is 2.71 (1.95–3.75). SMR before 1990 (continuous line) is 3.33 (1.64–6.75). SMR after 1990 (discontinuous lines) is 2.42 (1.89–3.11). Forest plot. Meta-regression of change in SMR (lnSMR) with mid-cohort year (Coefficient b = –0.055 and p = 0.064). Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

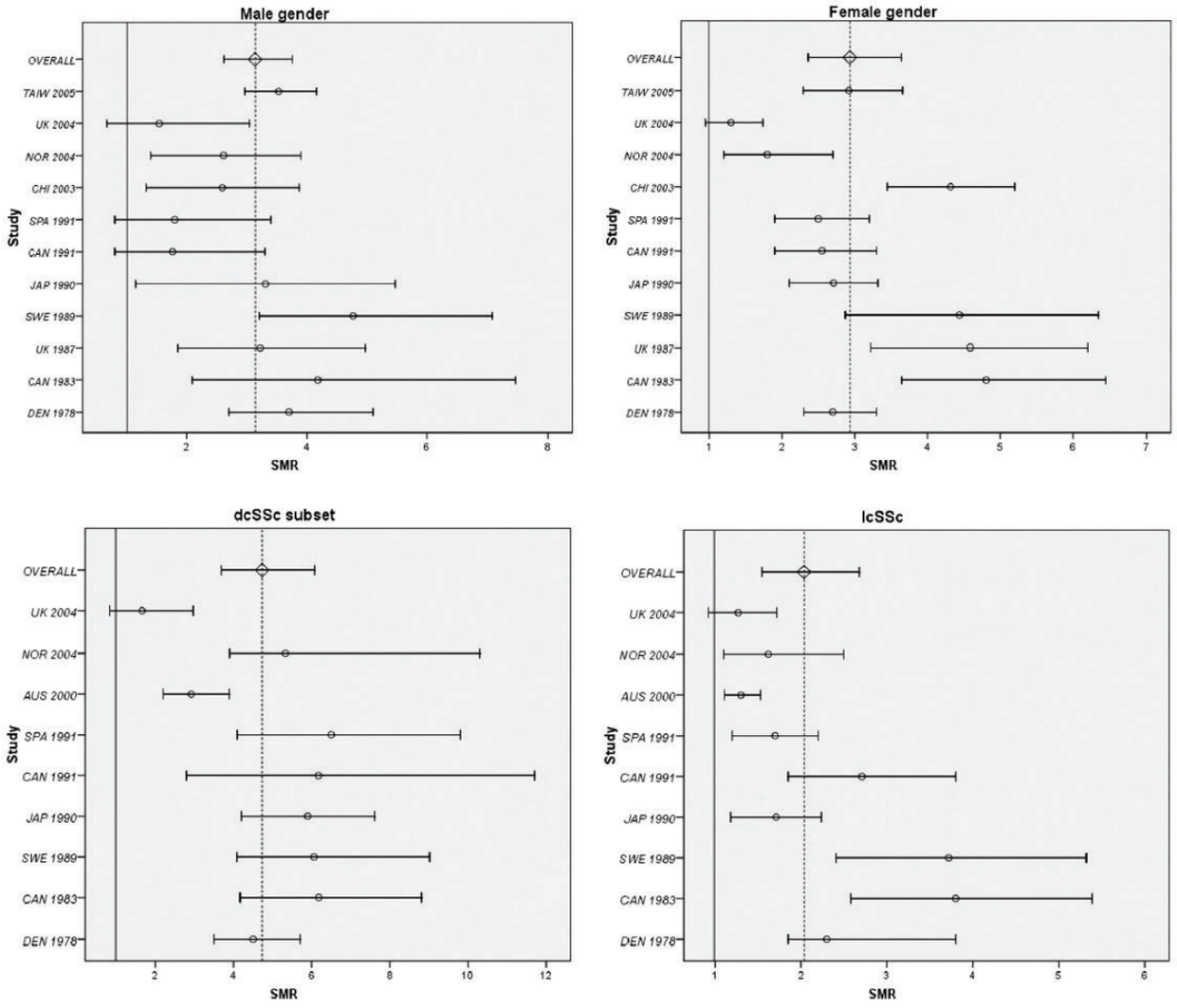

Figure 3. SMR meta-analysis. For the male gender, overall SMR is 3.18 (2.62–3.85) and for the female gender, overall SMR is 2.81 (2.25–3.50); for dcSSc subtype, the overall SMR is 4.73 (3.69–6.07) and for lcSSc subtype, overall SMR is 2.04 (1.55–2.68). Forest plot. Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

4. Causes of death

As in other autoimmune diseases, the pattern of mortality has been changing over time since the autoimmune disease by itself has been the main cause of death in these patients for ages but the more physicians control the disease, the more likely it is to die due to other causes not directly related to SSc [43, 54–56].

4.1. SSc-related causes of death

Among the SSc-related causes, there are four major organs potentially involved: the lungs, heart, kidneys and gastrointestinal tract. Among them, lung and renal involvement were the most important as a cause of death during the twentieth century (**Table 5**) [2, 3, 7, 8, 11–13, 15, 17–19, 21–24, 26, 29, 31, 33–42, 48, 50–53, 56, 57, 59–62].

4.1.1. Lung involvement

In the case of lung involvement, death can be due to the progression towards respiratory failure due to PAH or interstitial lung disease (ILD).

In the case of PAH, evidence suggests that SSc-PAH patients have a worse response to therapy when compared to idiopathic PAH. New therapies (phosphodiesterase type 5 inhibitors and endothelin receptor antagonists) have improved its prognosis but not that much and thus, this is still a severe manifestation of the disease and a frequent cause of death. An early combination schedule of treatment has been suggested to be better in terms of prognosis. However, more studies are required to demonstrate and standardize this strategy of treatment [63].

Interstitial lung disease constitutes the most severe manifestation of the disease and is in fact the first cause of death in these patients (**Figure 4**). Therefore, it is crucial to perform a regular screening of this involvement and an early treatment when diagnosed. Patients showing the following criteria would warrant an immunosuppressive treatment: (1) either an extent of lung disease >20% on High-resolution computed tomography (HRCT) or an indeterminate extent (disease extent not readily classifiable as minimal or severe; HRCT extent is 10–30%) of disease plus an FVC < 70%, (2) patients experiencing a significant decrease in pulmonary functional assessment during the follow-up (FVC > 10% or DLco >15% or both, whatever the extent of lung involvement is for 12 months). Currently, the management of SSc–ILD is largely confined to immunomodulvation. Non-selective immunosuppressants such as cyclophosphamide followed by mycophenolate mofetil and azathioprine are still the most widely used medications in SSc-ILD. Several alternative approaches may be considered, including B cell depletion therapies (rituximab), anti-TGF-β antibody, tyrosine kinase inhibitors (imatinib, dasatinib), anti-IL-6 antibody, anti-IL-13 antibody, pirfenidone and haematopoietic stem cell transplantation (HSCT). Finally, lung transplantation may be limited to those patients, with severe SSc-ILD, unresponsive to pharmacologic therapy [64]. It is important to remember that, although often used, during the first stages of treatment, prednisone doses over 15 mg a day can be dangerous in order to trigger a scleroderma renal crisis.

4.1.2. Renal involvement

Scleroderma renal crisis occurs during the rapid progression of skin thickening in the early stages of dcSSc (<5 years after disease onset). Several case series published during the past 20 years and a 2013 systematic literature review has estimated that SRC develops in 5–15 and 15% of patients with dcSSc, respectively. Interestingly, the incidence and prevalence of SRC seem to be decreasing over time, possibly as a result of early recognition and management of SRC risk factors and early signs and symptoms in patients with dcSSc [65]. The introduction of ACE inhibitors (captopril) reduced dramatically its frequency as the cause of death since early 1990s of the past century (**Figure 4**). Besides, its incidence is decreasing but due to unknown reasons. The extended use of ACE inhibitors prescribed for other reasons (i.e. arterial hypertension or heart failure) has not been found as the cause of this decreasing incidence.

	Country	Years (mid-cohort year)	Deads/n	SSc-related death	Lung death	Heart death	Kidney death	GI death
Farmer [2]	US	1945–1952 (48)	115/271 (49%)	17 (14.8%)	5 (29.4%)	6 (35.3%)	1 (5.9%)	1 (5.9%)
Bennet [3]	UK	1947–1970 (58)	26/67 (38.8%)	1 (9.1%)	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)
Rowell [7]	UK	1960–1975 (67)	22/84 (26.2%)	NA	NA	NA	NA	NA
Barnett [8]	AUS	1953–1983 (68)	86/177 (48.6%)	42 (48.8%)	8 (19%)	10 (11.6%)	16 (38.1%)	8 (9.3%)
Altman [11]	US	1973–1977 (75)	131/264 (49.6%)	89 (68%)	19 (21.3%)	19 (21.3%)	35 (39.3%)	13 (14.6%)
Eason [12]	NZ	1970–1980 (75)	24/47 (51%)	18 (75%)	7 (38.9%)	4 (22.2%)	5 (27.8%)	2 (11.1%)
Wynn [13]	US	1970–1980 (75)	25/64 (39.1%)	17 (68%)	7 (41.2%)	6 (35.3%)	4 (23.5%)	0 (0%)
Ferri [15]	ITA	1955–1999 (77)	279/1012 (27.6%)	61 (35.9%)	NA	NA	NA	NA
Lally [16]	US	1972–1984 (78)	17/91 (18.7%)	14 (82.4%)	0 (0%)	8 (57.1%)	6 (42.9%)	0 (0%)
Jacobsen [17]	DEN	1960–1996 (78)	160/344 (46.5%)	41 (25.6%)	13 (31.7%)	1 (2.4%)	17 (41.5%)	9 (22%)
Kuwana [18]	JAP	1971–1990 (80)	51/275 (18.5%)	32 (62.7%)	23 (71.9%)	4 (12.5%)	5 (15.6%)	0 (0%)
Geirsson [19]	ICE	1975–1990 (82)	5/23 (21.7%)	2 (40%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Abu-Shakra [48]	CAN	1976–1990 (83)	61/237 (25.7%)	44 (77.1%)	13 (29.5%)	5 (11.4%)	5 (11.4%)	0 (0%)
Nishioka [21]	JAP	1974–1994 (84)	90/496 (18.1%)	64 (71.1%)	44 (68.8%)	31 (48.4%)	12 (18.8%)	13 (20.3%)
Steen [56]	US	1972–1996 (84)	364/1508 (24.1%)	182 (50%)	NA	NA	NA	NA
Simeón [22]	SPA	1976–1996 (86)	12/79 (15.2%)	11 (91.7%)	4 (36.4%)	0 (0%)	7 (63.6%)	0 (0%)
Bulpitt [23]	US	1982–1992 (87)	15/48 (31.3%)	9 (60%)	4 (44.4%)	1 (11.1%)	4 (44.4%)	0 (0%)
Bryan [24]	UK	1982–1992 (87)	55/283 (19.4%)	34 (61.8%)	15 (44.1%)	5 (14.7%)	5 (14.7%)	3 (8.8%)
Geirsson [57]	SWE	1982–1995 (88)	30/100 (30%)	10 (33.3%)	5 (50%)	4 (40%)	1 (10%)	0 (0%)
Hesselstrand [26]	SWE	1983–1995 (89)	49/249 (19.7%)	15 (30.6%)	10 (66.7%)	1 (6.7%)	1 (6.7%)	3 (20%)
Bond [58]	AUS	1983–1996 (89)	123/123 (100%)	43 (35%)	13 (30.2%)	14 (32.6%)	6 (14%)	NA

	Country	Years (mid-cohort year)	Deads/n	SSc-related death	Lung death	Heart death	Kidney death	GI death
Vlachoyiannopoulos [59]	GRE	1982–1996 (89)	7/254 (2.8%)	6 (85.7%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0 (0%)
Hashimoto [29]	JAP	1973–1908 (90)	86/405 (21.2%)	NA	NA	NA	NA	NA
Scussel-Lonzetti [50]	CAN	1984–1999 (91)	66/309 (21.4%)	35 (53%)	6 (17.1%)	4 (11.4%)	7 (20%)	3 (8.6%)
Alamanos [31]	GRE	1981–2002 (91)	36/109 (33%)	23 (63.9%)	21 (58.3%)	21 (58.3%)	2 (5.6%)	0 (0%)
Joven [33]	SPA	1980–1906 (93)	44/204 (21.6%)	36 (82%)	20 (55.6%)	8 (22.2%)	1 (2.8%)	3 (8.3%)
Ruangjutipopan [34]	THAI	1987–2001 (94)	31/222 (26.7%)	18 (58.1%)	NA	NA	NA	0 (0%)
Czirják [35]	HUN	1983—2005 (94)	93/366 (25.4%)	86 (92.5%)	30 (34.9%)	29 (33.7%)	16 (18.6%)	8 (9.3%)
Derk [60]	US	1985–2007 (96)	87/87 (100%)	67 (77%)	65 (97%)	55 (82.1%)	2 (3%)	0 (0%)
Arias-Núñez [36]	SPA	1988–2006 (97)	20/78 (25.6%)	11 (55%)	10 (90.9%)	1 (9.1%)	0 (0%)	0 (0%)
Alba [37]	SPA	1986–2010 (98)	151/1037 (14.6%)	61 (78.2%)	NA	13 (16.7%)	0 (0%)	5 (4.1%)
Al-Dhaher [38]	CAN	1994–2004 (99)	42/185 (23%)	NA	15 (45.5%)	9 (27.3%)	9 (27.3%)	0 (0%)
Sampaio-Barros [39]	BRA	1991–2010 (00)	168/947 (17.7%)	110 (65.5%)	53 (48.2%)	27 (24.5%)	12 (10.9%)	5 (4.5%)
Assassi [61]	US	1998–2008 (03)	52/250 (20.8%)	29 (55.8%)	10 (34.5%)	4 (13.8%)	NA	2 (6.9%)
Mok [52]	CHI	1999–2008 (03)	110/449 (24.5%)	26 (24%)	11 (42.3%)	NA	5 (19.2%)	2 (7.7%)
Hoffmann-Vold [40]	NOR	1999–2009 (04)	43/312 (13.8%)	13 (54.2%)	0 (0%)	5 (20.8%)	6 (25%)	2 (4.7%)
Vettori [41]	ITA	2000–2008 (04)	20/251 (8%)	12 (60%)	5 (41.7%)	4 (33.3%)	1 (8.3%)	2 (16.7%)
Hachulla [62]	FR	2002–2006 (04)	47/546 (8.6%)	24 (51.1%)	19 (79.2%)	0 (0%)	3 (12.5%)	2 (8.3%)
Strickland [53]	UK	1999–2010 (04)	53/204 (26%)	19 (35.9%)	9 (47.4%)	4 (21.1%)	0 (0%)	1 (5.3%)
Kuo [42]	TAIW	2002–2007 (05)	204/1479 (13.8%)	57 (27.9%)	9 (4.4%)	29 (0.1%)	14 (6.9%)	10 (5%)

Lung, heart, kidney and GI are deaths related to SSc. NA: non-available; GI: gastrointestinal. Reprinted from Rubio-Rivas et al. [43], with permission from Elsevier.

Table 5. SSc-related causes of death in medical literature [43].

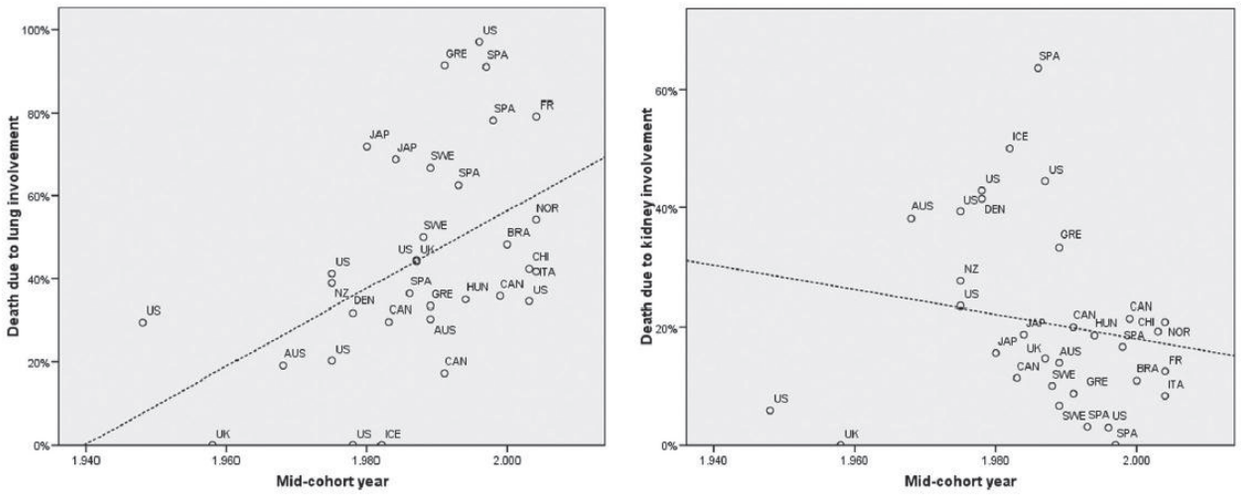

Figure 4. Meta-regression of deaths due to lung over time (coefficient b = 0.935 and p = 0.005) and renal (coefficient b=−0.206 and p = 0.352). Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

4.1.3. Heart involvement

Despite the fact that definite SSc for cardiac involvement does not exist, we could categorize its involvement in five major groups: pericarditis with or without cardiac tamponade, ischemic cardiopathy (documented myocardial infarction, angina, ischemic alterations in myocardial perfusion SPECT or requirement of coronary revascularization, surgical or percutaneous), pacemaker bearing regardless of the time of arrhythmia, sudden death and congestive heart failure [66]. As it is more recognized nowadays, its ratio is increasing, but the real challenge in the years to come shall be to distinguish the real scleroderma involvement from a cardiac SSc-non-related involvement. Anyway, we can hypothesize today that this is related to SSc in younger patients without classical cardiovascular risk factors.

4.1.4. Gastrointestinal involvement

The gastrointestinal tract is the most affected organ after the skin and can be affected from the oral cavity to the anus. About 90% of all patients will be affected during follow-up. This involvement can result in a decreased quality of life more often than a direct cause of death. In fact, it has been a rare cause of death over time. The few fatal cases have been related to those with severe intestinal involvement leading to malabsorption and secondary starvation. We cannot forget the possible role of the oesophageal involvement in the development of interstitial lung disease [67].

4.2. SSc-non-related causes of death

Among SSc-non-related causes of death, we can find three major diseases: cancer, infections and cardiovascular diseases (**Table 6**) [2, 3, 7, 8, 11–13, 15, 17–19, 21–24, 26, 29, 31, 33–42, 48, 50–53, 56, 57, 59–62].

	Country	Years (mid-cohort)	Deads/n	Cancer death	Infection death	Atherosclerosis death
Farmer [2]	US	1945–1952 (48)	115/271 (49%)	6 (5.2%)	4 (3.5%)	20 (17.4%)
Bennet [3]	UK	1947–1970 (58)	26/67 (38.8%)	2 (18.2%)	3 (27.3%)	5 (45.5%)
Rowell [7]	UK	1960–1975 (67)	22/84 (26.2%)	0 (0%)	NA	1 (4.5%)
Barnett [8]	AUS	1953–1983 (68)	86/177 (48.6%)	NA	NA	NA
Altman [11]	US	1973–1977 (75)	131/264 (49.6%)	9 (6.9%)	3 (2.3%)	17 (13%)
Eason [12]	NZ	1970–1980 (75)	24/47 (51%)	2 (8.3%)	2 (8.3%)	2 (8.3%)
Wynn [13]	US	1970–1980 (75)	25/64 (39.1%)	3 (12%)	0 (0%)	3 (12%)
Ferri [15]	ITA	1955–1999 (77)	279/1012 (27.6%)	25 (14.7%)	NA	
Lally [16]	US	1972–1984 (78)	17/91 (18.7%)	1 (5.9%)	2 (11.8%)	0 (0%)
Jacobsen [17]	DEN	1960–1996 (78)	160/344 (46.5%)	30 (18.8%)	19 (11.9 %)	43/160
Kuwana [18]	JAP	1971–1990 (80)	51/275 (18.5%)	5 (9.8%)	1 (2%)	5 (9.8%)
Geirsson [19]	ICE	1975–1990 (82)	5/23 (21.7%)	1 (20%)	0 (0%)	2 (40%)
Abu-Shakra [48]	CAN	1976–1990 (83)	61/237 (25.7%)	6 (9.8%)	0 (0%)	NA
Nishioka [21]	JAP	1974–1994 (84)	90/496 (18.1%)	21 (23.3%)	5 (5.6%)	NA
Steen [56]	US	1972–1996 (84)	364/1508 (24.1%)	63 (17.3%)	32 (8.8%)	30 (8.2%)
Simeón [22]	SPA	1976–1996 (86)	12/79 (15.2%)	1 (8.3%)	0 (0%)	0 (0%)
Bulpitt [23]	US	1982–1992 (87)	15/48 (31.3%)	1 (6.7%)	1 (6.7%)	0 (0%)
Bryan [24]	UK	1982–1992 (87)	55/283 (19.4%)	1 (1.8%)	4 (7.3%)	11 (20%)
Geirsson [57]	SWE	1982–1995 (88)	30/100 (30%)	9 (30%)	6 (20%)	3 (10%)
Hesselstrand [26]	SWE	1983–1995 (89)	49/249 (19.7%)	12 (24.5%)	9 (18.4%)	9 (18.4%)
Bond [58]	AUS	1983–1996 (89)	123/123 (100%)	10 (8.1%)	6 (4.9%)	17 (13.8%)
Vlachoyiannopoulos [59]	GRE	1982–1996 (89)	7/254 (2.8%)	0 (0%)	0 (0%)	0 (0%)
Hashimoto [29]	JAP	1973–2008 (90)	86/405 (21.2%)	19 (22.1%)	14 (16.3%)	NA
Scussel-Lonzetti [50]	CAN	1984–1999 (91)	66/309 (21.4%)	13 (19.7%)	NA	10 (15.2%)
Alamanos [31]	GRE	1981–2002 (91)	36/109 (33%)	4 (11.1%)	1 (0.2%)	6 (16.7%)
Joven [33]	SPA	1980–2006 (93)	44/204 (21.6%)	3 (6.8%)	2 (4.5%)	5 (11.4%)
Ruangjutipopan [34]	THAI	1987–2001 (94)	31/222 (26.7%)	0 (0%)	13 (42%)	0 (0%)
Czirják [35]	HUN	1983–2005 (94)	93/366 (25.4%)	12 (12.9%)	2 (2.2%)	NA
Derk [60]	US	1985–2007 (96)	87/87 (100%)	3 (4.5%)	4.6%	0 (0%)
Arias-Núñez [36]	SPA	1988–2006 (97)	20/78 (25.6%)	1 (5%)	3 (15%)	2 (10%)
Alba [37]	SPA	1986–2010 (98)	151/1037 (14.6%)	61 (78.2%)	18 (14.8%)	NA
Al-Dhaher [38]	CAN	1994–2004 (99)	42/185 (23%)	NA	NA	NA
Sampaio-Barros [39]	BRA	1991–2010 (00)	168/947 (17.7%)	8 (4.8%)	24 (14.3%)	8 (4.8%)

	Country	Years (mid-cohort)	Deads/n	Cancer death	Infection death	Atherosclerosis death
Assassi [61]	US	1998–2008 (03)	52/250 (20.8%)	NA	NA	NA
Mok [52]	CHI	1999–2008 (03)	110/449 (24.5%)	11 (10%)	19 (17.3%)	NA
Hoffmann-Vold [40]	NOR	1999–2009 (04)	43/312 (13.8%)	13 (54.2%)	6 (14%)	4 (9.3%)
Vettori [41]	ITA	2000–2008 (04)	20/251 (8%)	2 (10%)	1 (5%)	2 (10%)
Hachulla [63]	FR	2002–2006 (04)	47/546 (8.6%)	8 (17%)	4 (8.5%)	2 (4.3%)
Strickland [53]	UK	1999–2010 (04)	53/204 (26%)	10 (18.9%)	13(24.5%)	12 (22.6%)
Kuo [42]	TAIW	2002–2007 (05)	204/1479 (13.8%)	30 (14.7%)	12 (5.9%)	29 (14.2%)

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Table 6. SSc-non-related causes of death in medical literature [43].

4.2.1. Cancer

A higher standardized incidence ratio (SIR) of cancer in these patients not only compared to the general population that could be related to immunosuppressive treatment but also to the self-nature of the disease has been described [68]. In fact, those cancers diagnosed within the first 3 years after the diagnosis of scleroderma have been suggested to be classified as SSc-related causes. Cancer among SSc patients with RNA polymerase III antibodies has been reported to be in a close temporal relationship to the onset of SSc (first 36 months after the onset of SSc), which supports the paraneoplastic phenomenon in this subset of patients [69]. Thus, it is recommended to rule out this possibility at the time of the diagnosis, although protocol for this purpose has not been standardized so far. Cancers most frequently found in SSc patients are those from breast, blood, lung, gastrointestinal tract, genitourinary tract and skin and, out of these, those most related to the presence of RNAp III antibodies were breast cancer, skin cancer and genitourinary cancer [69].

4.2.2. Infections

Risk factors associated with infections in patients diagnosed with scleroderma include oesophageal (increased risk for aspiration pneumonia) and interstitial lung disease (increased risk for pneumonia), severe Raynaud's phenomenon or calcinosis (risk for localized super-infections) and the use of specific treatments for the management of the disease. Bacterial infections due to Gram-positive bacilli have been described, especially in patients with severe Raynaud or calcinosis. In patients receiving immunosuppressive treatment, especially corticosteroids, *Nocardia* sp. and *Mycobacteria* sp. must be taken into account. A few viruses such as *Epstein-Barr virus* and *CMV* have been described as triggering the onset of scleroderma, and *Parvovirus B19* DNA has been detected in patients who have scleroderma, but the clinical correlate of this finding is unclear. Finally, among fungi, *Pneumocystis jirovecii* pneumonia has been reported in some patients who have scleroderma [70]. *Aspergillus* sp. has been rarely reported in scleroderma, but in any patient under cellular immunosuppression has to be taken into account as well [71].

4.2.3. Cardiovascular disease

Scleroderma, as other autoimmune diseases, shows up as an inflammatory background that leads to the fibroblast activation. This background is more visual in the first stages of the skin or lung involvement, but it is thought to happen elsewhere. Thus, scleroderma itself can be understood as a new cardiovascular risk factor not only involved in the development of microvascular disease but also of macrovascular disease [72]. Atherosclerosis has been found to be increased in patients with SSc in all territories: coronary arteries, carotid arteries, cerebrovascular vessels and peripheral arteries [72]. This is the most controversial group of diseases in terms of classification since it is a challenge to differentiate whether it is an SSc-related or a SSc-non-related event. Although sometimes undistinguishable, currently, the clinical context has been hypothesized to aid for this purpose. Thus, in young patients without other classical cardiovascular risk factors (smoking behaviour, diabetes mellitus, arterial hypertension, hyperlipidaemia, obesity), we state that a particular event should be classified as SSc-related.

According to the latest studies [43], the big picture when talking about causes of death should be that SSc-related death is estimated nowadays in 56.7% of all deaths. Among them, representing lung death 57%, heart death 28.2%, renal death 11.7% and gastrointestinal death 6.4% (**Table 7**). In contrast, SSc-non-related death is estimated in 43.3% of all patients and among them being cancer, infections and cardiovascular disease the leading cause of SSc-non-related death.

4.3. A temporary pattern of SSc-related causes of death

In general, we could state that early death within the first years after the diagnosis of scleroderma is primarily due to the autoimmune disease itself, and late death is due to SSc-non directly related causes. Besides, this progression is currently even more notorious since data from the Spanish Registry show the fact that beyond 10 years after diagnosis, 83% of all deaths are due to SSc-non-related causes, supporting the idea that by struggling with the disease in the first years could save quite a few deaths due to the self-disease [54, 55].

	Before 1990 (22 studies)	After 1990 (18 studies)	p
SSc-related deaths % mean (SD)	52.5 (24.7)	56.7 (17.4)	0.544
Lung	34.5 (21.3)	57.0 (24.7)	0.008
Heart	29.3 (23.8)	28.2 (28.1)	0.905
Kidney	26.4 (17.6)	11.7 (7.9)	0.003
GI	6.8 (8.7)	6.4 (7.0)	0.881

T-test for independent groups among studies before and after 1990 (mid-cohort year). GI: gastrointestinal. Reprinted from Rubio-Rivas et al. [43], with permission from Elsevier.

Table 7. SSc-related causes of death [43].

Among these SSc-related causes, pulmonary death (due to ILD or PAH) has been and still currently is the leading SSc-related cause of death in all stages of the disease. In contrast, renal death was the second cause of the death in the past and most of all in the dcSSc subset and within the first 5 years after SSc diagnosis, but, in the last years, we have been witnesses of an important decrease of renal death rate. Heart death is at first sight more present nowadays and within the early stages of the disease but possibly due to a better understanding and knowledge of this involvement. Gastrointestinal death has been the cause of death only inisolated cases over time (**Table 8**).

Thus, it is expected to see an increasing rate of SSc-non-related causes in the years to come, mainly cancer and cardiovascular causes. Among the SSc-related causes, cardiovascular causes will be the cornerstone and the challenge will be to distinguish SSc-related and SSc-non-related cardiovascular events.

	Cause of death	1990–1999	2000–2009	p
Early	**SSc-non-related**	3 (17.6%)	23 (48.9%)	**0.042**
	Pulmonary	8 (47.1%)	16 (34.0%)	0.390
	Renal	6 (35.3%)	1 (2.1%)	**< 0.001**
	Cardiac	0 (0.0%)	7 (14.9%)	0.175
	Gastrointestinal	0 (0.0%)	0 (0.0%)	–
Intermediate	**SSc-non-related**	5 (23.8%)	11 (50.0%)	0.116
	Pulmonary	13 (61.9%)	6 (27.3%)	**0.033**
	Renal	1 (4.8%)	1 (4.5%)	1.000
	Cardiac	2 (9.5%)	4 (18.2%)	0.664
	Gastrointestinal	0 (0.0%)	0 (0.0%)	–
Late	**SSc-non-related**	10 (37.0%)	5 (83.3%)	**0.070**
	Pulmonary	11 (40.7%)	1 (16.7%)	0.379
	Renal	1 (3.7%)	0 (0.0%)	1.000
	Cardiac	4 (14.8%)	0 (0.0%)	1.000
	Gastrointestinal	1 (3.7%)	0 (0.0%)	1.000

Early (first 5 years after diagnosis), intermediate (5–10 years after diagnosis) and late death (>10 years after diagnosis) from the Spanish Scleroderma Network. Reprinted from Rubio-Rivas [54].

Table 8. SSc-non-related and SSc-related (lung, heart, renal and gastrointestinal) causes of death. In bold, p-values reaching statistical significance or close to significance.

5. Risk factors of poor outcome

To date, several risk factors have been identified related to poor prognosis, sometimes reported as a result of univariate analysis and sometimes as a result of multivariate analysis [43].

Taking into account the number of citations from the different studies (**Figure 5**), more cited risk factors would be an older age at diagnosis, dcSSc subset, male gender and visceral involvement (most of all lung, heart and renal involvement).

It is not easy to quantify the overall risk attributed to any of these factors since they have been described in different ways, but by meta-analysing those described homogeneously (**Figure 6**), we could state a hazard ratio for kidney involvement 4.22 (3.42–5.19), for heart involvement 3.43 (1.35–8.70), for ILD 2.89 (2.24–3.72), for high eritrosedimentation rate 2.77 (2.06–3.71), for PAH 2.62 (1.64–4.17), for dcSSc 2.28 (1.69–3.08), for male gender 1.88 (1.48–2.38) and age/year 1.05 (1.04–1.06) [43].

New risk factors are required in order to identify those patients with worse prognosis who could get some benefits in terms of a more aggressive therapy and/or closer follow-up. Recently, the mode of onset has been evaluated as a potential risk factor, finding a worse prognosis in those patients with an onset in the form of non-Raynaud's phenomenon, with the only exception of arthralgia (data not yet released).

Anyway, the risk should be individualized and accordingly lead to the decision-making for every patient. Thus, it should be our aim to create prognosis scales based on these known risk factors.

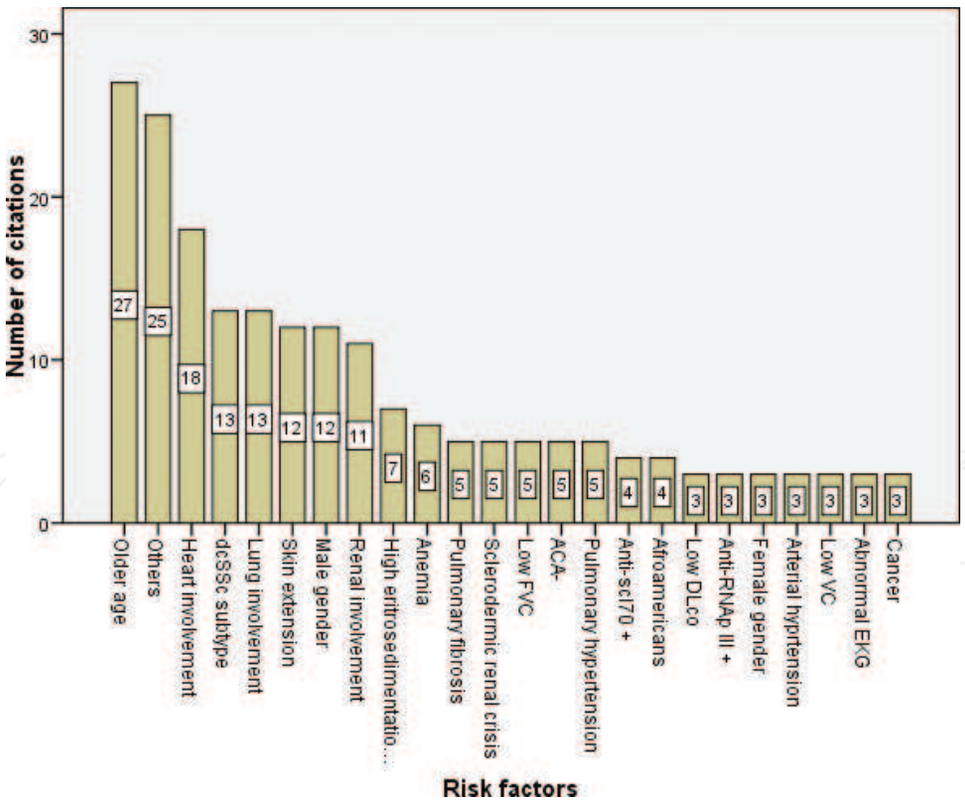

Figure 5. Risk factors for poor outcomes (number of citations in the different studies). Into "others" are included proteinuria, gastrointestinal and osteoarticular involvement, high BUN, hypo/hyperpigmentation, digital ulcers, HLADQA1 and HLA DRB1, low body mass index, hands deformity, low STC and low total lung compliance, myositis, anti-RNP +, S3 heart gallop, corticosteroid treatment, longer time from first Raynaud, no CREST, tobacco and alcohol uptake and hypoproteinaemia. Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

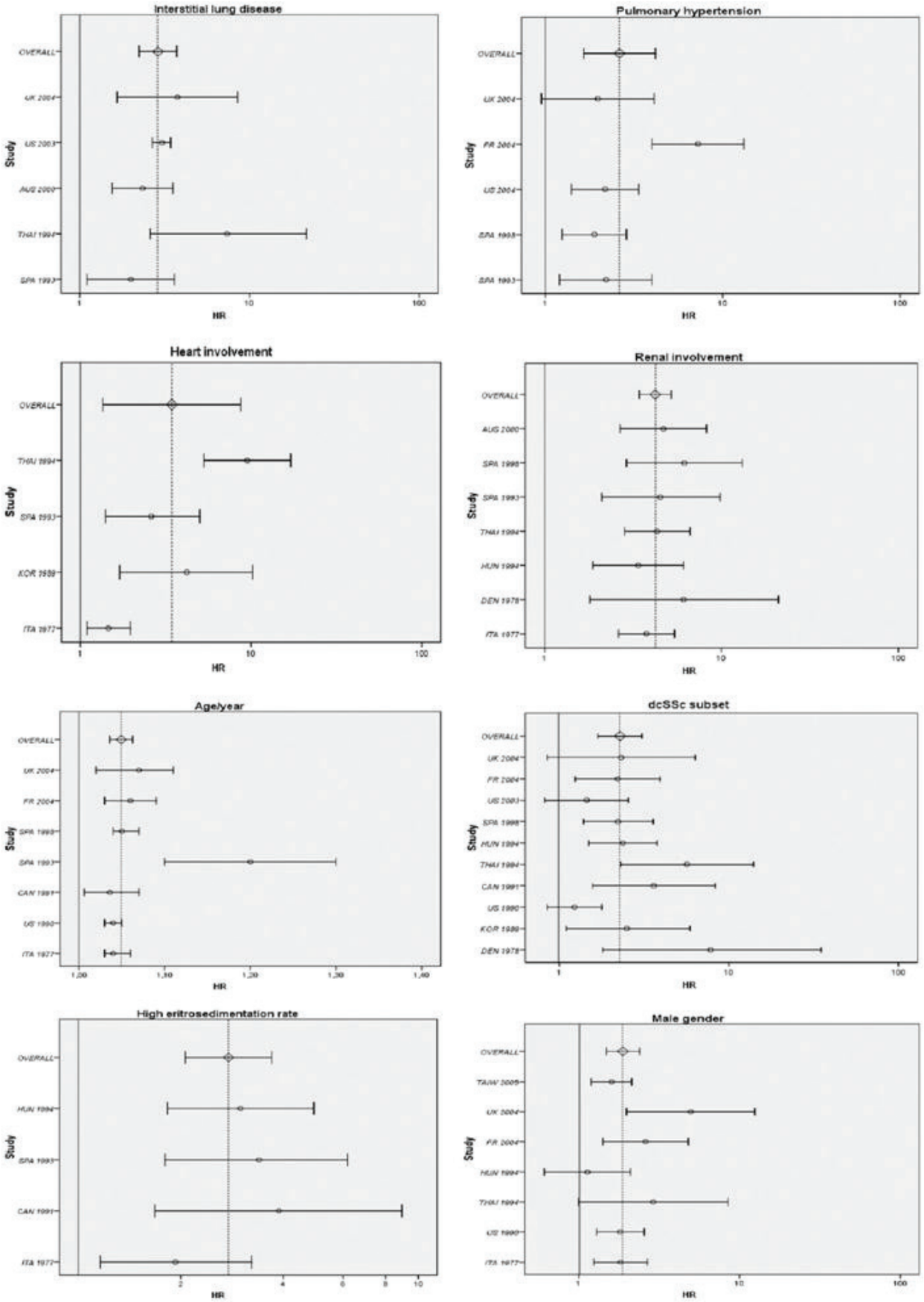

Figure 6. A quantitative meta-analysis of the main risk factors related to mortality. Reprinted from Rubio-Rivas et al., with permission from Elsevier [43].

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