

ORIGINAL INVESTIGATIONS

Appendix 1

Search strategy

Date: May 14, 2025

PubMed search strategy:

Number of publications retrieved: 823

Search: (((mortality) OR (standardized mortality ratio)) OR (survival)) AND (systemic sclerosis) AND (skin)

("mortality" [MeSH Terms] OR "mortality" [All Fields] OR "mortalities" [All Fields] OR "mortality" [MeSH Subheading] OR ("reference standards" [MeSH Terms] OR ("reference" [All Fields] AND "standards" [All Fields]) OR "reference standards" [All Fields] OR "standardization" [All Fields] OR "standard" [All Fields] OR "standard's" [All Fields] OR "standardization" [All Fields] OR "standardizations" [All Fields] OR "standardize" [All Fields] OR "standardized" [All Fields] OR "standardizes" [All Fields] OR "standardizing" [All Fields] OR "standardization's" [All Fields] OR "standardizations" [All Fields] OR "standardize" [All Fields] OR "standardized" [All Fields] OR "standardizes" [All Fields] OR "standardizing" [All Fields] OR "standards" [MeSH Subheading] OR "standards" [All Fields]) AND ("mortality" [MeSH Terms] OR "mortality" [All Fields] OR "mortalities" [All Fields] OR "mortality" [MeSH Subheading]) AND ("ratio" [All Fields] OR "ratio's" [All Fields] OR "ratios" [All Fields] OR "ratios" [All Fields])) OR ("mortality" [MeSH Subheading] OR "mortality" [All Fields] OR "survival" [All Fields] OR "survival" [MeSH Terms] OR "survivability" [All Fields] OR "survivable" [All Fields] OR "survivals" [All Fields] OR "survive" [All Fields] OR "survived" [All Fields] OR "survives" [All Fields] OR "surviving" [All Fields])) AND ("scleroderma, systemic" [MeSH Terms] OR ("scleroderma" [All Fields] AND "systemic" [All Fields]) OR "systemic scleroderma" [All Fields] OR ("systemic" [All Fields] AND "sclerosis" [All Fields]) OR "systemic sclerosis" [All Fields]) AND ("skin" [MeSH Terms] OR "skin" [All Fields])

Translations

mortality: "mortality" [MeSH Terms] OR "mortality" [All Fields] OR "mortalities" [All Fields] OR "mortality" [Subheading]

standardized: "reference standards" [MeSH Terms] OR ("reference" [All Fields] AND "standards" [All Fields]) OR "reference standards" [All Fields] OR "standardization" [All Fields] OR "standard" [All Fields] OR "standard's" [All Fields] OR "standardization" [All Fields] OR "standardizations" [All Fields] OR "standardize" [All Fields] OR "standardized" [All Fields] OR "standardizes" [All Fields] OR "standardizing" [All Fields] OR "standardization's" [All Fields] OR "standardizations" [All Fields] OR "standardize" [All Fields] OR "standardized" [All Fields] OR "standardizes" [All Fields] OR "standardizing" [All Fields] OR "standards" [Subheading] OR "standards" [All Fields]

mortality: "mortality" [MeSH Terms] OR "mortality" [All Fields] OR "mortalities" [All Fields] OR "mortality" [Subheading]

ratio: "ratio" [All Fields] OR "ratio's" [All Fields] OR "ratios" [All Fields] OR "ratios" [All Fields]

survival: "mortality" [Subheading] OR "mortality" [All Fields] OR "survival" [All Fields] OR "survival" [MeSH Terms] OR "survivability" [All Fields] OR "survivable" [All Fields] OR "survivals" [All Fields] OR "survive" [All Fields] OR "survived" [All Fields] OR "survives" [All Fields] OR "surviving" [All Fields]

systemic sclerosis: "scleroderma, systemic" [MeSH Terms] OR ("scleroderma" [All Fields] AND "systemic" [All Fields]) OR "systemic scleroderma" [All Fields] OR ("systemic" [All Fields] AND "sclerosis" [All Fields]) OR "systemic sclerosis" [All Fields]

skin: "skin" [MeSH Terms] OR "skin" [All Fields]

Date: May 14, 2025

EMBASE search strategy:

Number of publications retrieved: 2101

"systemic sclerosis"/exp AND ("skin"/exp OR "cutis" OR "derma" OR "human skin" OR "skin" OR "skin layer") AND ("mortality"/exp OR "mortality" OR "mortality model" OR "survival"/exp OR "death"/exp OR "death" OR "demise" OR "lethal outcome" OR "mors")

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Appendix 2

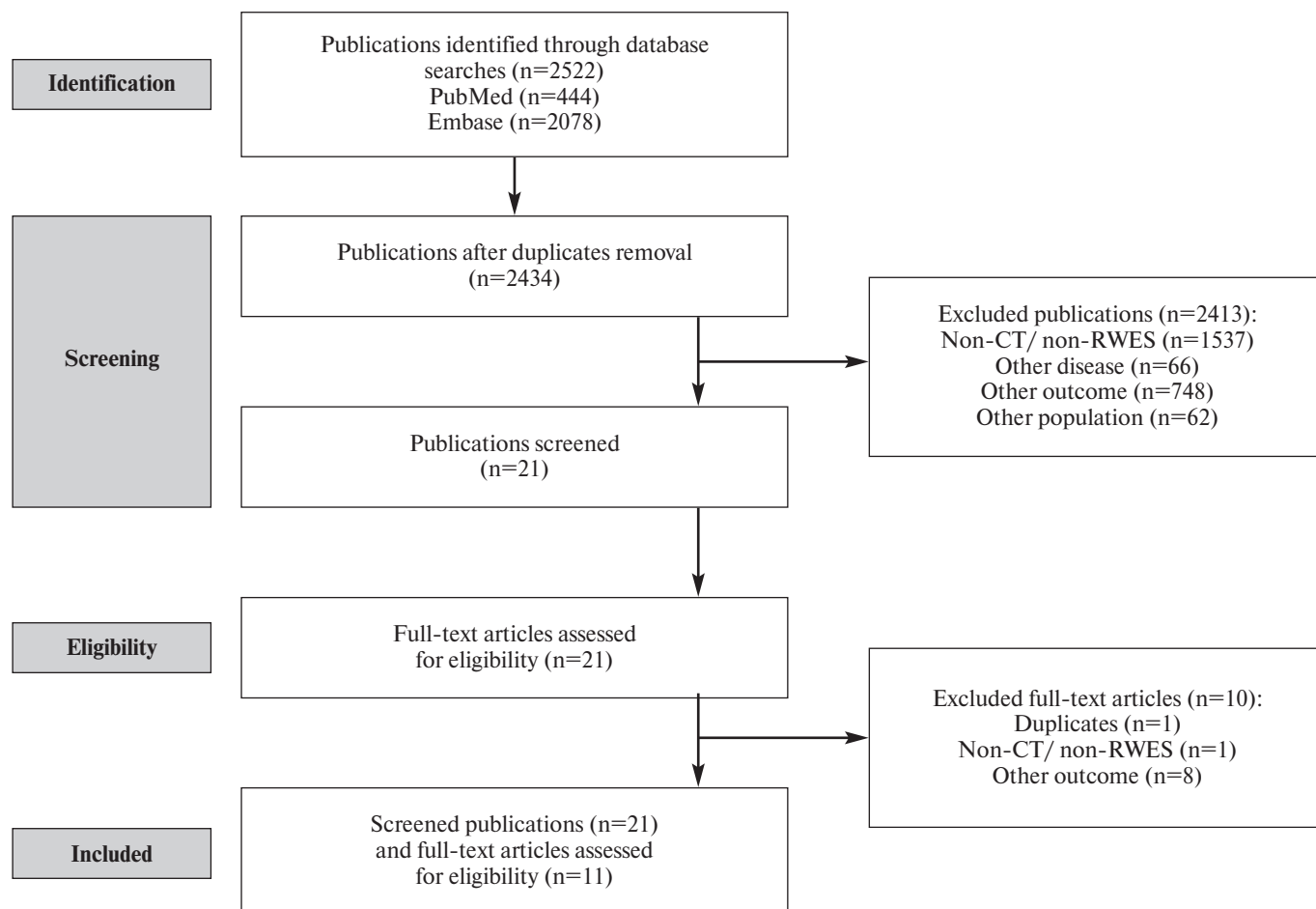


Fig. 4. PRISMA flow diagram. Publication selection scheme. CT/RWCP – clinical trial/real-world clinical practice study

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Appendix 3

Included publications

1. Ferri C, Valentini G, Cozzi F, et al; Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)*. 2002 Mar;81(2):139-53. doi: 10.1097/00005792-200203000-00004.
2. Geirsson AJ, Wollheim FA, Akesson A. Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. *Ann Rheum Dis*. 2001 Dec;60(12):1117-22. doi: 10.1136/ard.60.12.1117.
3. Perez-Bocanegra C, Solans-Laquerre R, Simeon-Aznar CP, et al. Age-related survival and clinical features in systemic sclerosis patients older or younger than 65 at diagnosis. *Rheumatology (Oxford)*. 2010 Jun;49(6):1112-7. doi: 10.1093/rheumatology/keq046.
4. Hesselstrand R, Andreasson K, Wuttge DM, et al. Increased serum COMP predicts mortality in SSc: results from a longitudinal study of interstitial lung disease. *Rheumatology (Oxford)*. 2012 May;51(5):915-20. doi: 10.1093/rheumatology/ker442.
5. Scussel-Lonzetti L, Joyal F, Raynauld JP, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine (Baltimore)*. 2002 Mar;81(2):154-67. doi: 10.1097/00005792-200203000-00005.
6. Hissaria P, Lester S, Hakendorf P, et al. Survival in scleroderma: results from the population-based South Australian Register. *Intern Med J*. 2011 May;41(5):381-90. doi: 10.1111/j.1445-5994.2010.02281.x.
7. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). *Br J Rheumatol*. 1998 Jul;37(7):750-5. doi: 10.1093/rheumatology/37.7.750.
8. Zafonitis CJD, Dabich L, Negri D, et al. Retrospective studies in scleroderma: effect of potassium para-aminobenzoate on survival. *J Clin Epidemiol*. 1988;41(2):193-205. doi: 10.1016/0895-4356(88)90094-7.
9. Bryan C, Howard Y, Brennan P, et al. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. *Br J Rheumatol*. 1996 Nov;35(11):1122-6. doi: 10.1093/rheumatology/35.11.1122.
10. Simeon CP, Armadans L, Fonollosa V, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. *Rheumatology (Oxford)*. 2003 Jan;42(1):71-5. doi: 10.1093/rheumatology/keg033.
11. Joven BE, Almodovar R, Carmona L, Carreira PE. Survival, causes of death, and risk factors associated with mortality in Spanish systemic sclerosis patients: results from a single university hospital. *Semin Arthritis Rheum*. 2010 Feb;39(4):285-93. doi: 10.1016/j.semarthrit.2009.06.002

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Appendix 4

Table 2. Characteristics of patient populations according to included studies

Author and year	Subgroup	Study start year	Study end year	Cohort mean year	Total follow-up period, patient-years	Mean age, years	Disease duration, years	Age at onset, years	Number of patients, N	Proportion, n/N (%)	Limited form, n/N (%)	Diffuse form, n/N (%)	Lung involvement, n/N (%)	Cardiac involvement, n/N (%)	Renal involvement, n/N (%)	Esophageal involvement, n/N (%)	ANA, n/N (%)	Anti-Scl70, n/N (%)	Anti-RNAP, n/N (%)	Overlap, n/N (%)
C. Ferri et al., 2002 [17]	All	1955	1999	1977	7185,2	50,5 (13,8)*	5,1 (7,3)*		1012	897/1012 (88,6)	822/1012 (81,2)	190/1012 (18,8)	607/1012 (60,0)	304/1012 (30,0)	71/1012 (7,0)		202/1012 (20,0)	364/1012 (36,0)		
C.J.D. Zaza-fonelis et al., 1988 [24]	All	1948	1980	1964	3394,6	45,5 (14,5)*			390	318/390 (81,5)	390/390 (100,0)		69/390 (17,7)	235/390 (60,1)	14/390 (3,6)	235/390 (60,3)				
S. Jacobsen et al., 1998 [23]	All	1960	1996	1978	3716,0		8,6 [0,0; 36,0]**	52,0 [9,0; 87,0]**	344	278/344 (80,8)	226/344 (65,7)	118/344 (34,3)	88/344 (25,6)							
R. Hesselstrand et al., 2012 [21]	Limited form					49,8 (14,3)*	1,4 (1,1)*		132	110/132 (83,3)			97/132 (73,5)			43/132 (32,6)		9/132 (6,8)	12/132 (9,1)	
R. Hesselstrand et al., 2012 [21]	Diffuse form					51,8 (1,3)*	1,3 (1,0)*		86	57/86 (66,3)			64/86 (74,4)			3/86 (3,5)		21/86 (24,4)	19/86 (22,1)	
R. Hesselstrand et al., 2012 [21]	All	1984	2009	1996	2182,4				218				161/218 (73,9)							
C. Bryan et al., 1996 [25]	All	1982	1993	1987	1871,0	46,0 (14,0)*			283	218/283 (77,0)	153/283 (54,1)	130/283 (45,9)	151/283 (53,4)							
A.J. Geirsson et al., 2001 [19]	All	1982	1995	1988	770,0			42,4	100	67/100 (67,0)	66/100 (66,0)	34/100 (34,0)	34/100 (34,0)							
P. Hissaria et al., 2011 [22]	All	1993	2007	2000	12 890,4	46,7 (16,2)*			786	630/786 (80,2)										
P. Hissaria et al., 2011 [22]	Limited form					48,1 (13,8)			501		501/501 (100,0)		19/501 (3,8)			278/501 (55,5)		12/501 (2,4)		

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Author and year	Subgroup	Study start year	Study end year	Cohort mean year	Total follow-up period, patient-years	Mean age, years	Disease duration, years	Age at onset, years	Number of patients, N	Proportion of women, n/N (%)	Limited form, n/N (%)	Diffuse form, n/N (%)	Lung involvement, n/N (%)	Cardiac involvement, n/N (%)	Renal involvement, n/N (%)	Esophageal involvement, n/N (%)	ANA, n/N (%)	Anti-Scl70, n/N (%)	Anti-RNAP, n/N (%)	Overlap, n/N (%)
P. Hissaria et al., 2011 [22]	Diffuse cutaneous form					47,3 (16,5)*			152			152/152 (100,0)	25/152 (16,4)				3/152 (2,0)	48/152 (31,6)		
P. Hissaria et al., 2011 [22]	Overlap forms					37,5 (15,7)*			53				3/53 (5,7)				6/53 (11,3)	2/53 (3,8)		53/53 (100,0)
B.E. Joven et al., 2010 [15]	All	1980	2006	1993	1635,0	49,0 (17,0)*	6,0 (10,0)*		204	182/204 (89,2)	121/204 (59,3)	62/204 (30,4)	78/204 (38,2)			75/204 (36,8)		46/204 (22,5)		21/204 (10,3)
B.E. Joven et al., 2010 [15]	Limited form					53,0 (17,0)*	7,0 (10,0)*		121	113/121 (93,4)			30/121 (24,8)			67/121 (55,4)		16/121 (13,2)		
B.E. Joven et al., 2010 [15]	Diffuse form					46,0 (16,0)*	5,0 (9,0)*		62	52/62 (83,9)			38/62 (61,3)			6/62 (9,7)		29/62 (46,8)		
B.E. Joven et al., 2010 [15]	Overlap forms					39,0 (10,0)*	3,0 (5,0)*		21	17/21 (81,0)			10/21 (47,6)			2/21 (9,5)		1/21 (4,8)		
C. Perez-Bocanegra et al., 2010 [20]	All	1976	2007	1991	5344,8				319		186/319 (58,3)	64/319 (20,1)	244/319 (76,5)			127/319 (39,8)		55/319 (17,2)		
C. Perez-Bocanegra et al., 2010 [20]	Age >65 years					71,7	6,9 (5,6)*		67	61/67 (91,0)	50/67 (74,6)	5/67 (7,5)	58/67 (86,6)			28/67 (41,8)		6/67 (9,0)		
C. Perez-Bocanegra et al., 2010 [20]	Age <65 years					11,0 (7,5)*			252		136/252 (54,0)	59/252 (23,4)	186/252 (73,8)			99/252 (39,3)		49/252 (19,4)		
L. Scussell-Lonzetti et al., 2002 [18]	All	1984	1999	1991	2187,3				309	266/309 (86,1)										

ORIGINAL INVESTIGATIONS

Author and year	Subgroup	Study start year	Study end year	Cohort mean year	Total follow-up period, patient-years	Mean age, years	Disease duration, years	Age at onset, years	Number of patients, N	Proportion of women, n/N (%)	Limited form, n/N (%)	Diffuse form, n/N (%)	Lung involvement, n/N (%)	Cardiac involvement, n/N (%)	Renal involvement, n/N (%)	Esophageal involvement, n/N (%)	ACA, n/N (%)	ANA, n/N (%)	Anti-Scl70, n/N (%)	Anti-RNAP, n/N (%)	Overlap, n/N (%)
L. Scussell-Lonzetti et al., 2002 [18]	Normal skin						8,0 (11,0)*	38,0 (13,0)*	50	46/50 (92,0)			1/50 (2,0)				25/50 (50,0)				
L. Scussell-Lonzetti et al., 2002 [18]	Limited form						11,0 (11,0)*	40,0 (14,0)*	152	132/152 (86,8)			11/152 (7,2)				75/152 (49,3)		16/152 (10,5)		
L. Scussell-Lonzetti et al., 2002 [18]	Intermediate form						9,0 (11,0)*	41,0 (14,0)*	78	67/78 (85,9)			14/78 (17,9)				27/78 (34,6)		10/78 (12,8)		
L. Scussell-Lonzetti et al., 2002 [18]	Diffuse form						3,0 (4,0)*	44,0 (14,0)*	29	21/29 (72,4)			8/29 (27,6)				1/29 (3,4)		4/29 (13,8)		
C.P. Simeon et al., 2003 [16]	All	1976	1996	1986	481,8	48,8 [15,4; 73,0]**	4,5	44,2 [7,0; 72,6]**	79	68/79 (86,1)	57/79 (72,2)	22/79 (27,8)	35/79 (44,3)	8/79 (10,1)	69/79 (87,3)	25/79 (31,6)			15/79 (19,0)		
C.P. Simeon et al., 2003 [16]	Diffuse form						1,0		22												
C.P. Simeon et al., 2003 [16]	Limited form					4,7		57													

Note. ACA = anticentromere antibodies; ANA = antinuclear antibodies; anti-Scl70 = antibodies to topoisomerase I; anti-RNAP = antibodies to RNA polymerase III. * Data are presented as M (SD); ** Data are presented as Me [25th; 75th percentiles].

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Appendix 5

Table 3. Downloaded outcomes

Author and year	Log (SMR)	SE Log (SMR)	CMR	SE CMR	observed	Deaths expected	Total follow-up period, patient-years
C. Ferri et al., 2002 [17]	1,05	0,06	0,04	0,00	279,00	97,55	7185,20
C.J.D. Zarafonetis et al., 1988 [24]	1,69	0,08	0,04	0,00	142,00	26,30	3394,60
S. Jacobsen et al., 1998 [23]	1,07	0,08	0,04	0,00	160,00	54,80	3716,00
R. Hesselstrand et al., 2012 [21]	1,52	0,14	0,02	0,00	49,00	10,68	2182,40
C. Bryan et al., 1996 [25]	1,40	0,14	0,03	0,00	55,00	13,57	1871,00
A.J. Geirsson et al., 2001 [19]	1,28	0,18	0,04	0,01	30,00	8,34	770,00
P. Hissaria et al., 2011 [22]	0,38	0,07	0,03	0,00	331,00	226,71	12 890,40
B.E. Joven et al., 2010 [15]	1,13	0,34	0,03	0,00	44,00	14,19	1635,00
C. Perez-Bocanegra et al., 2010 [20]	0,62	0,12	0,01	0,00	73,00	39,38	5344,80
L. Scussel-Lonzetti et al., 2002 [18]	0,99	0,12	0,03	0,00	66,00	24,54	2187,30
C.P. Simeon et al., 2003 [16]	1,46	0,31	0,02	0,01	12,00	2,79	481,80

Appendix 6

Table 4. Assessment of the risk of bias in the included studies

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from planned interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
C. Ferri et al., 2002 [17]	Moderate	Moderate	Moderate	Serious	Moderate	Low	Low	Serious
S. Jacobsen et al., 1998 [23]	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
C.J.D. Zarafonetis et al., 1988 [24]	Low	Low	Low	NA	Moderate	Low	Low	Moderate
R. Hesselstrand et al., 2012 [21]	Serious	Moderate	Moderate	Moderate	Low	Low	Moderate	Serious
A.J. Geirsson et al., 2001 [19]	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious
C. Bryan et al., 1996 [25]	Low	Moderate	Low	NA	Low	Moderate	Low	Moderate
B.E. Joven et al., 2010 [15]	Moderate	Low	Moderate	Moderate	Low	Low	Low	Moderate
P. Hissaria et al., 2011 [22]	Moderate	Low	Moderate	Moderate	Serious	Low	Low	Serious
L. Scussel-Lonzetti et al., 2002 [18]	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate
C. Perez-Bocanegra et al., 2010 [20]	Serious	Moderate	Low	NA	Moderate	Low	Low	Serious
C.P. Simeon et al., 2003 [16]	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate

Note. Bias = Systematic error; NA = Not available.

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Appendix 7

Table 5. Result of sensitivity analysis using the leave-one-out method

LOO-method	SMR	I ² , %	Annual CMR per 1,000 patients	I ² , %
All studies	3,1 (2,4–4,1)	95,4	29,4 (24,2–35,8)	90,5
Без С. Ferri et al., 2002 [17]	3,1 (2,3–4,3)	95,7	28,5 (23,0–35,3)	89,8
Без С. J.D. Zarfionetis et al., 1988 [24]	2,9 (2,3–3,7)	93,4	28,3 (23,0–34,7)	90,1
Без С. Jacobsen et al., 1998 [23]	3,1 (2,3–4,3)	95,7	28,2 (23,0–34,5)	89,5
Без R. Hesselstrand et al., 2012 [21]	3,0 (2,2–4,0)	95,5	30,2 (24,6–37,1)	90,9
Без С. Bryan et al., 1996 [25]	3,0 (2,3–4,0)	95,6	29,4 (23,8–36,3)	91,4
Без A.J. Geirsson et al., 2001 [19]	3,1 (2,3–4,1)	95,8	28,7 (23,4–35,3)	91,3
Без Р. Hissaria et al., 2011 [22]	3,3 (2,7–4,1)	87,6	29,8 (24,0–37,2)	89,8
Без В.Е. Joven и et al., 2010 [15]	3,1 (2,3–4,2)	95,8	29,7 (24,1–36,5)	91,3
Без С. Perez-Bocanegra et al., 2010 [20]	3,3 (2,4–4,4)	95,6	32,1 (27,4–37,6)	83,7
Без L. Scussel-Lonzetti et al., 2002 [18]	3,1 (2,3–4,2)	95,8	29,3 (23,7–36,2)	91,3
Без С.Р. Simeon et al., 2003 [16]	3,0 (2,3–4,0)	95,8	29,7 (24,3–36,4)	91,4

Note. Data are presented as central tendency (95% CI); I² is a parameter of heterogeneity.

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Appendix 8

Table 6. Sensitivity analysis results for meta-regression

Sensitivity analysis option	Annual CMR per 1,000 patients univariate	Annual CMR per 1,000 patients bivariate	SMR univariate	SMR bivariate
All studies	26,0 (17,2–39,2)	26,1 (17,3–39,3)	4,2 (2,6–6,5)	4,2 (2,6–6,5)
Excluding follow-up calculation	29,4 (14,0–61,8)	29,5 (14,1–61,6)	5,9 (3,1–11,4)	5,8 (3,0–11,3)
Excluding imputation of lung involvement proportion	14,2 (0,6–351,8)	14,7 (0,6–364,3)	24,2 (1,0–565,6)	23,2 (1,0–521,1)
Excluding intermediate cutaneous form and overlap	26,2 (17,8–38,6)	25,8 (17,1–39,0)	4,0 (3,3–5,0)	4,0 (3,3–4,9)
Excluding C. Ferri et al., 2002 [17]	26,2 (18,4–37,2)	26,6 (18,6–38,2)	4,2 (2,6–6,8)	4,2 (2,6–6,8)
Excluding C.J.D. Zarafonets et al., 1988 [24]	26,1 (17,6–38,7)	26,0 (17,5–38,7)	4,2 (2,9–6,0)	4,2 (2,9–6,0)
Excluding S. Jacobsen et al., 1998 [23]	25,8 (16,9–39,2)	25,8 (17,0–39,3)	4,1 (2,6–6,6)	4,1 (2,6–6,7)
Excluding R. Hesselstrand et al., 2012 [21]	26,8 (13,1–54,8)	26,8 (13,1–54,8)	4,8 (2,2–10,4)	4,8 (2,2–10,4)
Excluding C. Bryan et al., 1996 [25]	25,2 (14,3–44,4)	25,3 (14,4–44,5)	4,2 (2,3–7,9)	4,2 (2,3–7,9)
Excluding A.J. Geirsson et al., 2001 [19]	25,6 (16,6–39,4)	25,6 [16,6–39,5]	4,1 (2,5–6,5)	4,1 (2,5–6,5)
Excluding P. Hissaria et al., 2011 [22]	25,6 (17,5–37,5)	25,5 (17,4–37,4)	4,0 (3,0–5,5)	4,0 (3,0–5,5)
Excluding B.E. Joven et al., 2010 [15]	26,3 (16,9–40,8)	26,4 (17,0–40,8)	4,1 (2,5–6,7)	4,1 (2,5–6,7)
Excluding C. Perez-Bocanegra et al., 2010 [20]	26,8 (20,0–36,0)	27,1 (20,5–35,8)	4,2 (2,8–6,5)	4,3 (2,8–6,6)
Excluding L. Scussel-Lonzetti et al., 2002 [18]	26,1 (16,9–40,3)	26,1 (16,9–40,3)	4,2 (2,6–6,7)	4,2 (2,6–6,7)
Excluding C.P. Simeon et al., 2003 [16]	26,2 (17,0–40,4)	26,2 (17,0–40,4)	4,1 (2,6–6,4)	4,1 (2,6–6,4)

Note. SA = Sensitivity analysis. Data are presented as central tendency (95% CI).