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ORIGINAL ARTICLE

Prevalence of the limited vs. extensive scleroderma-related interstitial lung disease at the time of diagnosis of SSc-ILD based on Goh et al. criteria. Systematic review and meta-analysis

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KEYWORDS
Scleroderma;
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Abstract
Introduction: Goh et al. proposed in 2008 a classificatory algorithm of limited or extensive SSc-ILD. The prevalence of both at the time of diagnosis of SSc-ILD is not known with exactitude.
Methods: The review was undertaken by means of MEDLINE and SCOPUS from 2008 to 2023 and using the terms: ÿsystemic¿ ÿsclerodermaör ïnterstitial lung disease[MesH]. The Newcastle-Ottawa Scale was used for the qualifying assessment for observational studies and the Jadad scale for clinical trials. The inverse variance-weighted method was performed.
Results: Twenty-seven studies were initially included in the systematic review and meta-analysis (SRMA). Of these, 17 studies had no overlapping data. They reported data from 2,149 patients, 1,369 (81.2%) were female. The mean age was 52.4 (SD 6.6) years. 45.2% of the patients had the diffuse subtype and 54.8% had the limited or sine scleroderma subtype. A total of 38.7% of the patients showed positive antitopoisomerase antibodies (ATA) and 14.2% positive anticentromere antibodies (ACA). The mean percentage of forced vital capacity (FVC) at baseline was 80.5% (SD 6.9) and of diffusing capacity of the lungs for carbon monoxide (DLco) was 59.1% (SD 9.6). Twelve studies presented SSc-ILD extension data adjusted for PFTs and were included in the meta-analysis. The 10 observational cohort studies were analyzed separately. The overall percentage of limited extension was estimated at 63.5% (95%CI 55.3–73; $p < 0.001$) using the random-effects model. Heterogeneity between studies (I^2) was 9.8% (95%CI 0–68.2%) with the random-effects model. Extensive pulmonary involvement was estimated at 34.3% (95%CI 26–45.4; $p < 0.001$). Heterogeneity between studies (I^2) was 0% (95%CI 0–61.6%) with the random-effects model.
Conclusion: The overall percentage of limited SSc-ILD at the time of diagnosis of SSc-ILD was estimated at 63.5% and extensive at 34.3%.

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PALABRAS CLAVE
Esclerodermia;
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Prevalencia;
Metaanálisis

Prevalencia de la enfermedad pulmonar esclerodermia-intersticial limitada frente a la extensa en el momento del diagnóstico de SSc-EPID según los criterios de Goh et al. Revisión sistemática y metanálisis

Resumen
Introducción: Goh et al. propusieron en 2008 un algoritmo clasificatorio de SSc-EPID limitada o extensa. La prevalencia de ambos en el momento del diagnóstico de SSc-EPID no se conoce con exactitud.
Métodos: La revisión se realizó mediante MEDLINE y SCOPUS desde 2008 hasta 2023 y utilizando los términos: s̈istémica, ës̈clerodermiaö ënfermedad pulmonar intersticial[MesH]. Se utilizó la escala de Newcastle-Ottawa para la evaluación de la calificación de los estudios observacionales y la escala de Jadad para los ensayos clínicos. Se realizó el método inverso ponderado por la varianza.
Resultados: Se incluyeron inicialmente 27 estudios en la revisión sistemática y metaanálisis (SRMA). De ellos, 17 estudios no tenían datos coincidentes. Comunicaron datos de 2.149 pacientes, 1.369 (81,2%) eran mujeres. La edad media era de 52,4 (DE 6,6) años. El 45,2% de los pacientes presentaban el subtipo difuso y el 54,8% el subtipo limitado o esclerodermia sinusal. El 38,7% de los pacientes presentaban anticuerpos antitopoisomerasa (ATA) positivos y el 14,2% anticuerpos anticentrómero (ACA) positivos. El porcentaje medio de capacidad vital forzada (FVC) al inicio del estudio fue del 80,5% (DE 6,9) y de capacidad de difusión pulmonar para el monóxido de carbono (DLco) fue del 59,1% (DE 9,6). Doce estudios presentaron datos de extensión de SSc-EPID ajustados por PFR y se incluyeron en el metaanálisis. Los 10 estudios observacionales de cohortes se analizaron por separado. El porcentaje global de afectación limitada se estimó en un 63,5% (IC 95%: 55,3−73; p < 0,001) utilizando el modelo de efectos aleatorios. La heterogeneidad entre estudios (I2) fue del 9,8% (IC95% 0−68,2%). La afectación pulmonar extensa se estimó en 34,3% (IC 95%: 26−45,4; p < 0,001). La heterogeneidad entre estudios (I2) fue del 0% (IC 95%: 0−61,6%) con el modelo de efectos aleatorios.
Conclusiones: El porcentaje global de SSc-EPID limitada en el momento del diagnóstico de SSc-EPID se estimó en un 63.5% y extensa en un 34.3%.

Introduction

Systemic Sclerosis (SSc) is an autoimmune systemic disease of unknown origin. Among the most serious affectations of the disease and currently the main cause of death is pulmonary involvement, either in the form of pulmonary hypertension (SSc-PAH) or diffuse interstitial involvement (SSc-ILD).[1,2] The latter occurs in about 60−91% of patients at some time during the disease, although it mainly appears in the first 5 years after the diagnosis of SSc.[3] Only in a small proportion of patients will SSc-ILD progress. These are known as progressors. However, it is not known for sure who they will be. Some risk factors for progression have been described, such as age, male sex, black race, diffuse subtype (dcSSc), positive antitopoisomerase antibodies (ATA), greater interstitial extension on high-resolution CT-scan (HRCT), and worse pulmonary function tests (PFTs).[4] In 2008, Goh et al. proposed an algorithm in which they classified patients with SSc-ILD into limited or extensive disease.[5] This predictive model was based on HRCT findings and PFTs. Increasingly extensive disease on HRCT was a powerful predictor of mortality with an optimal extent threshold of 20%. In patients with HRCT extent of 10−30% (termed indeterminate disease), an FVC threshold of 70% was an adequate prognostic substitute.

The exact prevalence of limited or extensive pulmonary involvement is not known for certain. The present study aimed to review the studies in SSc-ILD in which lung involvement has been classified according to the criteria of Goh et al. and to meta-analyze them in order to approach the true prevalence of both forms of parenchymal involvement.

Methods

The present study is a systematic review with meta-analysis (SRMA). The search was performed by two independent investigators (M.R-R. and M.P-F.) through the MEDLINE and SCOPUS databases between January 2008 and June 2023, using the terms: s̈ystemic, s̈clerodermaÄND ïnterstitial lung disease[MesH]. The search was completed by the literature review of each article selected for full-text review. No language-related restriction was performed. In the first search, 4,250 articles were found, of which 4,140 articles were not selected by assessing the title and/or abstract. One hundred and ten articles were finally selected for full-text review. We initially selected studies in SSc-ILD patients showing the percentage of patients with extensive or limited lung involvement at the diagnosis of SSc-ILD according to the 2008 Goh et al. criteria.[5] Subsequently, the 95% confidence interval was calculated according to Wilson's

Table 1 Studies included in the SRMA.

Study	Year	n	Country	Type of study	NOS	JADAD
Goh et al.[5]	2008	215	UK	Prospective cohort study	7	NA
Winklehner et al.[12]	2011	25	SWI	Prospective cohort study	6	NA
Moore et al.[13]	2013	172	AUS	Prospective cohort study	7	NA
Frauenfelder et al.[14]	2014	77	SWI	Prospective cohort study	7	NA
Iudici et al.[15]	2015	39	ITA	Open-label single-arm trial	NA	1
Khanna et al.[16]	2015	93	US	RCT	NA	5
Moore et al.[17]	2015	60	AUS	Prospective cohort study	7	NA
Ariani et al.[18]	2015	132	ITA	Prospective cohort study	8	NA
Yamakawa et al.[19]	2016	40	JAP	Retrospective cohort study	6	NA
Morriset et al.[20]	2017	89	US	Retrospective cohort study	6	NA
Hax et al.[21]	2017	101	BRA	Retrospective cohort study	6	NA
Le Gouellec et al.[22]	2017	75	FR	Prospective cohort study	7	NA
Goh et al.[23]	2017	162	UK	Retrospective cohort study	7	NA
Sircar et al.[24]	2018	60	IND	Open-label RCT	NA	3
Bocchino et al.[25]	2019	39	ITA	Prospective cohort study	6	NA
Forestier et al.[26]	2020	58	FR	Retrospective cohort study	6	NA
Ufuk et al.[27]	2020	55	TUR	Prospective cohort study	6	NA
Clukers et al.[28]	2021	35	US	Prospective cohort study	7	NA
Stock et al.[29]	2021	189	UK	Retrospective cohort study	6	NA
		118	UK	Prospective cohort study	7	NA
Vandecasteele et al.[30]	2021	243	BEL	Prospective cohort study	7	NA
Watanabe et al.[31]	2021	77	JAP	Prospective cohort study	7	NA
Martini et al.[32]	2021	60	SWI	Retrospective cohort study	6	NA
Schniering et al.[33]	2022	90	SWI	Prospective cohort study	7	NA
		66	NOR	Prospective cohort study	7	NA
Fairly et al.[34]	2023	479	AUS	Prospective cohort study	8	NA
Jang et al.[35]	2023	106	KOR	Retrospective cohort study	6	NA
Enghelmayer et al.[36]	2023	71	ARG	Retrospective cohort study	7	NA
Ramahi et al.[37]	2023	213	USA	Prospective cohort study	8	NA

NOS: Newcastle–Ottawa Scale. RCT: Randomized clinical trial. NA: Not available/applicable. SRMA: Systematic review and meta-analysis.

method.[6] Studies from the same country were reviewed to rule out overexpression of data.

Quality assessment was performed using the Newcastle–Ottawa scale (NOS) for observational studies and the Jadad scale for clinical trials.[7,8]

Statistical analysis

Categorical variables were described as absolute numbers and percentages. Continuous variables were described as mean and standard deviation (SD).

The inverse variance-weighted method was initially performed by using the fixed effects model. Thereafter, between-study variability was measured by the Tau^2 parameter and, when confirmed ($p \leq 0.05$), the analysis was completed by using the random effects model. The random effects model assumes that there is an underlying effect for each study which varies randomly across studies, with the resulting overall effect an average of these.[9,10] Initially, the calculation was performed for all the studies and, subsequently, only in the observational studies.

Publication bias was assessed using Egger's method.[11] Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Results

Studies included general data

Twenty-seven studies were initially included in the SRMA (Table 1 and 2).[5,12–37] Two of them[29,33] presented data from 2 substudies, so we can speak of 25 studies included. Of these, 22 were observational cohort studies (17 prospective and 8 retrospective)[5,12–37] and 3 were clinical trials.[15,16,24] The studies by Goh et al.[5,23] and the first substudy by Stock et al.[29] belong to the same cohort at the Royal Brompton Hospital in London, UK. The second study by Goh et al. and the first substudy by Stock et al. were removed from the meta-analysis for this reason. The studies by Moore et al.[13,17] and Fairly et al.[34] belong to the Australian Scleroderma Cohort Study (ASCS) and present overlapping patient data, so we have decided to include only the latter in the meta-analysis. The studies by Winklehner et al.,[12] Frauenfelder et al.,[14] Martini et al.,[32] and the first substudy by Schniering et al.[33] belong to the University Hospital of Zurich, Switzerland, and contain possibly overlapping patient data. We included the study by Schniering et al. in the initial data analysis. These 4 studies showed unadjusted data on the extent of SSc-ILD so neither was included in the meta-analysis. The studies by Le Gouellec et al.[22] and Forestier

Table 2 Sociodemographic features of the studies.

Study	Gender (female) n (%)	Mean age, Years (SD)	Mean disease duration, years (SD)	Subset dcSSc/lcSSc or sine scleroderma n (%)	ATA/ACA n (%)
Goh et al.[5]	174 (80.9)	49.1 (13)	NA	NA	NA
Winklehner et al.[12]	NA	NA	NA	NA	NA
Moore et al.[13]	138 (80.2)	NA	10.5 (10.1)[a]	65 (38)/98 (57)	56 (33.1)/22 (33.1)
Frauenfelder et al.[14]	NA	NA	NA	NA	NA
Iudici et al.[15]	41 (91)	49.7 (13.3)	11 (NA)[a]	5 (12.8)/34 (87.2)	27 (60)/9 (20)
Khanna et al.[16]	68 (73.1)	47.2 (11.7)	3.3 (2.2)[b]	56 (60.2)/37 (40)	22 (32.8)/14 (21)
Moore et al.[17]	NA	NA	NA	NA	NA
Ariani et al.[18]	NA	NA	NA	NA	NA
Yamakawa et al.[19]	34 (85)	61.7 (16.4)	NA	NA	11 (27.5)/13 (32.5)
Morriset et al.[20]	NA	NA	NA	NA	NA
Hax et al.[21]	83 (82.2)	51.8 (13.6)	7 (NA)[a]	35 (34.7)/66 (65.3)	26 (27.4)/22 (23.7)
Le Gouellec et al.[22]	57 (76)	52 (15.8)	6.7 (8.5)[a]	23 (31)/52 (69)	41 (55)/9 (12)
Goh et al.[23]	133 (82.1)	48 (13)	NA	63 (38.9)/99 (61.1)	70 (43)/NA
Sircar et al.[24]	50 (83)	36 (NA)	1.8 (NA)[a]	60 (100)/0	NA
Bocchino et al.[25]	37 (94.9)	56.5 (11.8)	NA	14 (35.9)/25 (64.1)	32 (82.1)/3 (7.7)
Forestier et al.[26]	39 (67.2)	54.5 (14.9)	4 (NA)[a]	26 (44.8)/32 (55.2)	38 (67.9)/10 (17.9)
Ufuk et al.[27]	45 (81.8)	55.6 (13.9)	2.6 (1.5)[b]	NA	NA
Clukers et al.[28]	22 (62.9)	51.6 (NA)	3.7 (3.2)[b]	31 (88.6)/4 (11.4)	11 (31.4)/3 (8.6)
Stock et al.[29]	146 (77.3)	49.1 (NA)	NA	74 (35.5)/115 (63.5)	85 (45)/20 (10.6)
	90 (76.3)	56.4 (NA)	NA	57 (35.5)/61 (63.5)	53 (44.9)/2 (1.7)
Vandecasteele et al.[30]	NA	NA	NA	NA	NA
Watanabe et al.[31]	58 (75.3)	56 (NA)	NA	59 (76.6)/18 (23.4)	40 (51.9)/NA
Martini et al.[32]	52 (86.7)	NA	NA	11 (18.3)/49 (81.7)	NA
Schniering et al.[33]	69 (76.7)	57.5 (17.8)	5 (8.2)[b]	42 (46.7)/48 (53.3)	41 (45.6)/13 (14.4)
	50 (75.8)	61 (18.8)	5.3 (9.2)[b]	29 (43.9)/37 (56.1)	24 (36.4)/7 (10.6)
Fairly et al.[34]	391 (81.6)	48 (NA)	6.9 (NA)[b]	176 (36.7)/303 (63.3)	152 (31.7)/87 (18.2)
Jang et al.[35]	92 (86.8)	51.9 (12.7)	NA	NA	60 (56.6)/6 (5.7)
Enghelmayer et al.[36]	67 (94.4)	NA	NA	27 (38)/44 (62.1)	17 (37)/11 (28.2)
Ramahi et al.[37]	NA	NA	NA	NA	NA

ATA: Antitopoisomerase antibody. ACA:Anticentromere antibodies. NA: Not available/applicable. SD: Standard deviation.
[a] Duration of the disease since the first symptom including Raynaud's phenomenon.
[b] Duration of the disease since the first symptom other than Raynaud's phenomenon.

et al.[26] are from Lille University Hospital, France, and show overlapping patient data. We have included only the study by Le Gouellec et al. in the meta-analysis. The study by Khanna et al.,[16] Clukers et al.,[28] and Ramahi et al.[37] belong to the same group from the University of Michigan. Only the first one was included in the meta-analysis. Finally, the studies by Iudici et al.[15] and Bocchino et al.[25] belong to the same Naples group. Only the former was included in the meta-analysis.

Thus, we finally had 17 studies, 3 clinical trials,[15,16,24] and 14 observational studies.[5,18–22,27,29–31,33–36] These reported data from 2,149 patients, 1,369 (81.2%) were female. The mean age was 52.4 (SD 6.6) years. As regards to the skin subset, 45.2% of the patients had the diffuse subtype and 54.8% had the limited or sine scleroderma subtype. A total of 38.7% of the patients showed positive antitopoisomerase

Table 3 ILD stage and PFTs at baseline.

Study	Unadjusted limited ILD disease n (%)	Adjusted limited ILD disease n (%)	Unadjusted extensive ILD disease n (%)	Adjusted extensive ILD disease n (%)	Baseline FVC, % predicted mean (SD)	Baseline DLco, % predicted mean (SD)
Goh et al.[5]	151 (70.2)	147 (68.4)	64 (29.8)	68 (31.6)	78.7 (21.4)	55.1 (16.8)
Winklehner et al.[12]	7 (28)	NA	18 (72)	NA	NA	NA
Moore et al.[13]	NA	122 (74)[a]	NA	42 (26)[a]	84.1 (17.4)	56.2 (15.2)
Frauenfelder et al.[14]	52 (67.5)	NA	25 (32.5)	NA	NA	NA
Iudici et al.[15]	NA	23 (59)	NA	16 (41)	81.5 (15.9)	51.5 (12)
Khanna et al.[16]	38 (44.7)	20 (22)[a]	47 (55.3)	71 (78)[a]	67.7 (11.9)	46.3 (12.8)
Moore et al.[17]	40 (33.3)	NA	20 (66.7)	NA	NA	NA
Ariani et al.[18]	NA	84 (63.6)	NA	48 (36.4)	NA	NA
Yamakawa et al.[19]	NA	19 (51.4)[a]	NA	18 (48.6)[a]	84 (20.6)	69.4 (19.4)
Morriset et al.[20]	59 (66)	NA	30 (34)	NA	NA	NA
Hax et al.[21]	60 (62.5)	NA	36 (37.5)	NA	74.9 (21.9)	50.2 (17.7)
Le Gouellec et al.[22]	NA	57 (76)	NA	18 (24)	90 (19.9)	67.2 (23.9)
Goh et al.[23]	NA	113 (69.8)	NA	49 (30.2)	79.6 (21.1)	56.2 (16.6)
Sircar et al.[24]	10 (17)	NA	50 (83)	NA	NA	NA
Bocchino et al.[25]	19 (48.7)	NA	20 (51.3)	NA	89.2 (26)	51.2 (18.9)
Forestier et al.[26]	NA	35 (59.7)	NA	23 (40.3)	96.4 (21.3)	70.1 (25.5)
Ufuk et al.[27]	NA	37 (67.3)	NA	18 (22.7)	84.8 (26.7)	67.4 (22.2)
Clukers et al.[28]	11 (44[a]	NA	14 (56)[a]	NA	78.4 (21.4)	69.5 (28.3)
Stock et al.[29]	NA	146 (77.2)	NA	43 (22.8)	80.1 (NA)	55.5 (NA)
	NA	46 (39)	NA	72 (61)	73.8 (NA)	39.9 (NA)
Vandecasteele et al.[30]	NA	207 (85)	NA	36 (15)	NA	NA
Watanabe et al.[31]	NA	51 (66.2)	NA	26 (33.8)	88.3 (NA)	59.5 (NA)
Martini et al.[32]	49 (81.7)	NA	11 (18.3)	NA	NA	NA
Schniering et al.[33]	50 (55.6)	NA	40 (44.4)	NA	87.5 (33.9)	66.5 (29.4)
	30 (45.5)	NA	36 (54.5)	NA	85 (36)	61 (29)
Fairly et al.[34]	NA	299 (69.1)[a]	NA	134 (30.9)[a]	NA	NA
Jang et al.[35]	NA	60 (56.6)	NA	46 (43.4)	71.9 (21.3)	65.3 (23.6)
Enghelmayer et al.[36]	36 (50.7)	NA	35 (49.3)	NA	78.3 (19.4)	68.6 (23.5)
Ramahi et al.[37]	103 (48.4)	NA	110 (51.6)	NA	NA	NA

FVC: Forced vital capacity. DLco: Diffusing capacity of the lungs for carbon monoxide. ILD: Interstitial lung disease. NA: Not available/applicable. PFTs: Pulmonary function tests. SD: Standard deviation.
[a] Studies with missing data in some patients.

antibodies (ATA) and 14.2% positive anticentromere antibodies (ACA).

Pulmonary function tests (PFTs)

Pulmonary function data are shown in Table 3. The mean percentage of forced vital capacity (FVC) at baseline was 80.5% (SD 6.9) and of diffusing capacity of the lungs for carbon monoxide (DLco) was 59.1% (SD 9.6).

Goh et al. algorithm across the studies

In total, 12 non-overlapping studies presented extension data adjusted for PFTs (Table 3).[5,15,16,18,19,22,27,29–31,34,35] These were the studies finally included in the quantitative meta-analysis. These studies reported data from 1,672 patients. The overall percentage of limited disease at the time of diagnosis of SSc-ILD was estimated at 60.4% (95%CI 53.5–68.1; p < 0.001) using the random-effects model. Egger's method: A = −4.647 p = 0.004. Heterogeneity between studies (I^2) was 91.5% (95%CI 87%–94.4%) with the fixed-effects model and 53.7% (95%CI 11%–75.9%) with the random-effects model. Extensive pulmonary involvement at the time of diagnosis of SSc-ILD was estimated at 37% (95%CI 28.2–48.7; p < 0.001). Egger's method: A = −5.723 p = 0.068. Heterogeneity between studies (I^2) was 95.2% (95%CI 93.1%–96.6%) with the fixed-effects model and 0% (0–51.4%) with the random-effects model.

After plotting using Galbraith's method (Fig S1 and S2) we excluded the study by Fairly et al. [34]. Recalculating, limited pulmonary involvement at the time of diagnosis of SSc-ILD was estimated at 58.7% (95%CI 50.5–68.3%; p < 0.001) using the random-effects model. Egger's method: A = −5.578 p = <0.001. Heterogeneity between studies (I^2) was 92.1% (95%CI 87.9%–94.9%) with the fixed-effects model and 43.9% (95%CI 0–72.2%) with the random-effects model. Extensive pulmonary involvement at the time of diagnosis of SSc-ILD was estimated at 37.7% (95%CI 28.2–50.5; p < 0.001). Egger's method: A = −7.703 p = 0.006. Heterogeneity between studies (I^2) was 95% (95%CI 92.2%–96.4%) with the fixed-effects model and 0% (95%CI 0–51.4%) with the random-effects model.

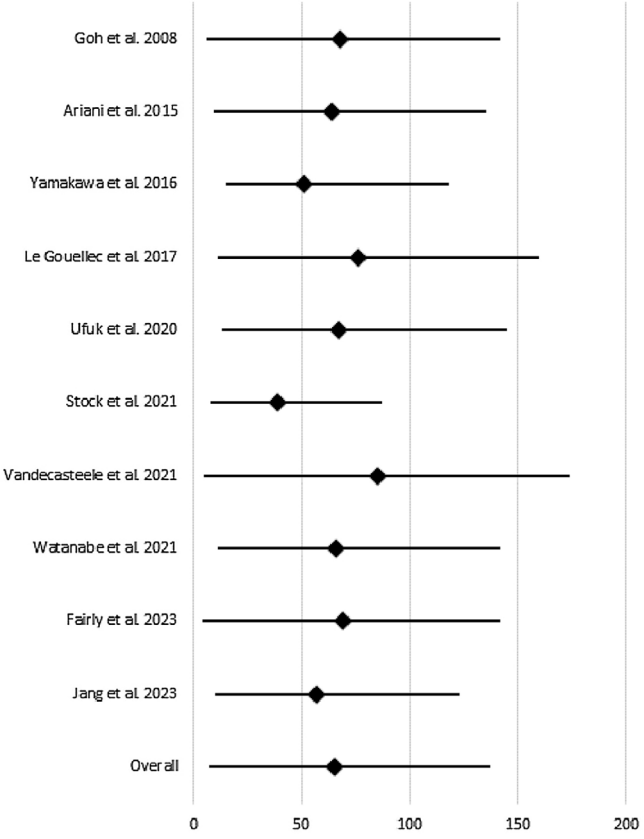

Figure 1 Percentage of patients with limited SSc-ILD in observational studies. Forest plot.

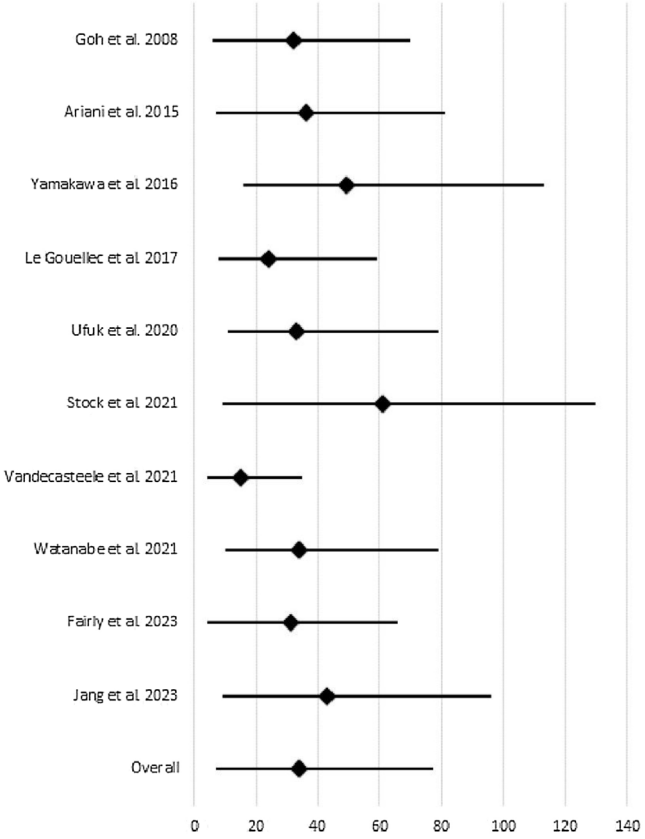

Figure 2 Percentage of patients with extensive SSc-ILD in observational studies. Forest plot.

To improve the homogeneity of the sample, the 10 observational cohort studies but the one by Fairly et al. were analyzed separately.[5,18,19,22,27,29–31,35] The overall percentage of limited extension was estimated at 63.5% (95%CI 55.3–73; p < 0.001) using the random-effects model. Egger's method: A = −5.408 p = 0.003. Heterogeneity between studies (I^2) was 90.7% (95%CI 84.5–94.4%) with the fixed-effects model and 9.8% (95%CI 0–68.2%) with the random-effects model. Extensive pulmonary involvement was estimated at 34.3% (95%CI 26–45.4; p < 0.001). Egger's method: A = −6.249 p = 0.064. Heterogeneity between studies (I^2) was 91.3% (95%CI 85.8%–94.7%) with the fixed-effects model and 0% (95%CI 0–61.6%) with the random-effects model (Figs. 1 and 2).

Discussion

The present study is the first SRMA to analyze the extent of SSc-ILD at the time of diagnosis of SSc-ILD based on the criteria of Goh et al.[5] It is not the aim of our study to know the actual prevalence of limited or extensive involvement in SSc-ILD over time. For that we would need a long follow-up period in the studies and adjust for the duration of SSc from the first symptom. Our aim is to estimate the percentage of patients with limited or extensive involvement in SSc-ILD at the time of diagnosis. It is therefore a real-life study. We want to know how many patients are candidates for treatment for their SSc-ILD at entry once diagnosed due to the extent of their interstitial lung pathology regardless of the duration of their SSc. We found a prevalence of limited interstitial lung involvement at the time of diagnosis of SSc-ILD in 63.5% of patients with SSc-ILD and extensive involvement in 34.3% of patients with SSc-ILD.

Some of the studies included in the systematic review did not show extension data adjusted for PFTs. They, therefore, did not follow the criteria of Goh et al. They have been included in the tables but not in the quantitative meta-analysis. Furthermore, the study by Sircar et al.[24] shows data only in the diffuse subtype population. As is well known, these patients present more interstitial involvement and greater progression of the same. Therefore, it is easy to think that the percentage of interstitial involvement is overestimated in this study. As it shows data not adjusted for PFTs, it has not been included in the quantitative meta-analysis.

The number of studies in SSc-ILD that do not show data referring to staging based on the criteria of Goh et al. or any other prognostic scale proposed to date is striking. This is surprising since it is the main criterion for deciding to initiate treatment in SSc-ILD. Not all patients with SSc-ILD are the same. Fortunately, only a small percentage of them will be progressors. Getting closer to predicting who they will give us valuable information that can help us target more aggressive therapies to that subgroup of patients. We believe that the method proposed by Goh et al. is practical and easy to implement. The diagnosis of SSc-ILD should be classified in this way and, in combination with other sociodemographic, clinical, and analytical data, allow us to

create a risk scale to direct treatment in this important visceral involvement. At the outset, we can say that at least 34% of newly diagnosed SSc-ILD patients need specific treatment for their SSc-ILD. In follow-up, a higher percentage will require it, they will be the p̈rogressorp̈atients. This would ideally be the subject of a new meta-analysis to estimate this percentage.

The study has clear strengths. It is the first SRMA to analyze the extent of interstitial lung involvement at the time of diagnosis of SSc-ILD based on the criteria of Goh et al. and is the best evidence to date of the extent of interstitial lung involvement in SSc. Secondly, the patient sample is large.

There are also some limitations of the study. First, there is between-study variability so the random effects model was chosen for the assessment. Secondly, the time of disease duration is different between studies and this fact may influence the extent of interstitial involvement. It would have been interesting to perform a meta-regression of pulmonary involvement according to the disease duration but we do not have sufficient data to perform such an analysis. Thirdly, there is heterogeneity among the studies. This fact has been minimized by performing the random effects model. Fourthly, Egger's method suggests some publication bias in the studies.

In conclusion, the prevalence of limited SSc-ILD at the time of diagnosis of SSc-ILD according to the criteria of Goh et al. is found in 63.5% of patients with SSc-ILD and extensive involvement in 34.3% of patients with SSc-ILD.

Competing interests and funding

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rceng.2024.02.008.

References

1. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007;66(7):940–4.
2. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44(2):208–19.
3. Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, Clements PJ, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. Chest. 2008;134(2):358–67.
4. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. Am J Respir Crit Care Med. 2020;201(6):650–60.
5. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008;177(11):1248–54.
6. Altman DG, Machin D, Bryant TN, Gardner MJ. Statistics with confidence. Confidence intervals and statistical guidelines. 2nd ed London: BMJ Books; 2000.
7. Wells G., Shea B., O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
9. Kahn HA, Sempos CT. Statistical Q14 methods in epidemiology. Oxford University Press; 1989.
10. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
12. Winklehner A, Berger N, Maurer B, Distler O, Alkadhi H, Frauenfelder T. Screening for interstitial lung disease in systemic sclerosis: the diagnostic accuracy of HRCT image series with high increment and reduced number of slices. Ann Rheum Dis. 2012;71(4):549–52.
13. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology (Oxford). 2013;52(1):155–60.
14. Frauenfelder T, Winklehner A, Nguyen TD, Dobrota R, Baumueller S, Maurer B, et al. Screening for interstitial lung disease in systemic sclerosis: performance of high-resolution CT with limited number of slices: a prospective study. Ann Rheum Dis. 2014;73(12):2069–73.
15. Iudici M, Cuomo G, Vettori S, Bocchino M, Zamparelli AS, Cappabianca S, et al. Low-dose pulse cyclophosphamide in interstitial lung disease associated with systemic sclerosis (SSc-ILD): efficacy of maintenance immunosuppression in responders and non-responders. *Semin Arthritis Rheum*. 2015;44(4):437–44.
16. Khanna D, Nagaraja V, Tseng CH, Abtin F, Suh R, Kim G, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. Arthritis Res Ther. 2015;17:372.
17. Moore OA, Proudman SM, Goh N, Corte TJ, Rouse H, Hennessy O, et al. Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease. Clin Exp Rheumatol. 2015;33 4 Suppl 91:S111–6.
18. Ariani A, Silva M, Bravi E, Saracco M, Parisi S, De Gennaro F, et al. Operator-independent quantitative chest computed tomography versus standard assessment of interstitial lung disease related to systemic sclerosis: a multi-centric study. Mod Rheumatol. 2015;25(5):724–30.
19. Yamakawa H, Hagiwara E, Kitamura H, Yamanaka Y, Ikeda S, Sekine A, et al. Clinical features of idiopathic interstitial pneumonia with systemic sclerosis-related autoantibody in comparison with interstitial pneumonia with systemic sclerosis. PLoS One. 2016;11(8):e0161908.
20. Morisset J, Vittinghoff E, Elicker BM, Hu X, Le S, Ryu JH, et al. Mortality risk prediction in scleroderma-related interstitial lung disease: the SADL model. Chest. 2017;152(5):999–1007.
21. Hax V, Bredemeier M, Didonet Moro AL, Pavan TR, Vieira MV, Pitrez EH, et al. Clinical algorithms for the diagnosis and prognosis of interstitial lung disease in systemic sclerosis. Semin Arthritis Rheum. 2017;47(2):228–34.
22. Le Gouellec N, Duhamel A, Perez T, Hachulla A-L, Sobanski V, Faivre J-B, et al. Predictors of lung function test severity and

outcome in systemic sclerosis-associated interstitial lung disease. PLoS One. 2017;12(8):e0181692.
23. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol*. 2017;69(8):1670–8.
24. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology (Oxford). 2018;57(12):2106–13.
25. Bocchino M, Bruzzese D, D'Alto M, Argiento P, Borgia A, Capaccio A, et al. Performance of a new quantitative computed tomography index for interstitial lung disease assessment in systemic sclerosis. Sci Rep. 2019;9(1):9468.
26. Forestier A, Le Gouellec N, Béhal H, Kramer G, Perez T, Sobanski V, et al. Evolution of high-resolution CT-scan in systemic sclerosis-associated interstitial lung disease: description and prognosis factors. Semin Arthritis Rheum. 2020;50(6):1406–13.
27. Ufuk F, Demirci M, Altinisik G. Quantitative computed tomography assessment for systemic sclerosis-related interstitial lung disease: comparison of different methods. Eur Radiol. 2020;30(8):4369–80.
28. Clukers J, Lanclus M, Belmans D, Van Holsbeke C, De Backer W, Vummidi D, et al. Interstitial lung disease in systemic sclerosis quantification of disease classification and progression with high-resolution computed tomography: an observational study. J Scleroderma Relat Disord. 2021;6(2):154–64.
29. Stock CJW, Hoyles RK, Daccord C, Kokosi M, Visca D, De Lauretis A, et al. Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. Respirology. 2021;26(5):461–8.
30. Vandecasteele E, Melsens K, Vanhaecke A, Blockmans D, Bonroy C, Carton C, et al. Incidence, prevalence and long-term progression of Goh algorithm rated interstitial lung disease in systemic sclerosis in two independent cohorts in flanders: a retrospective cohort study. Semin Arthritis Rheum. 2021;51(5):969–76.
31. Watanabe S, Kase K, Saeki K, Ohkura N, Murata A, Waseda Y, et al. Kinetic changes in serum KL-6 levels predict disease progression in patients with systemic sclerosis-associated interstitial lung disease. Respir Med. 2022;191:106689.
32. Martini K, Baessler B, Bogowicz M, Blüthgen C, Mannil M, Tanadini-Lang S, et al. Applicability of radiomics in interstitial lung disease associated with systemic sclerosis: proof of concept. Eur Radiol. 2021;31(4):1987–98.
33. Schniering J, Maciukiewicz M, Gabrys HS, Brunner M, Blüthgen C, Meier C, et al. Computed tomography-based radiomics decodes prognostic and molecular differences in interstitial lung disease related to systemic sclerosis. Eur Respir J. 2022;59(5):2004503.
34. Fairley JL, Hansen D, Ross L, Proudman S, Sahhar J, Ngian G-S, et al. Clinical characteristics and survival of pulmonary arterial hypertension with or without interstitial lung disease in systemic sclerosis. Arthritis Res Ther. 2023;25(1):77.
35. Jang HJ, Woo A, Kim SY, Yong SH, Park Y, Chung K, et al. Characteristics and risk factors of mortality in patients with systemic sclerosis-associated interstitial lung disease. Ann Med. 2023;55(1):663–71.
36. Enghelmayer JI, López Meiller MJ, Vallejos A, Felder F, Milena Pertuz M, Arias T, et al. Description of a single centre cohort of patients with systemic sclerosis from the University Hospital of Buenos Aires and factors associated with lung function deterioration. A retrospective study. Reumatol Clin. 2023;19:351–7.
37. Ramahi A, Lescoat A, Roofeh D, Nagaraja V, Namas R, Huang S, et al. Risk factors for lung function decline in systemic sclerosis-associated interstitial lung disease in a large single-centre cohort. Rheumatology (Oxford). 2023;62(7):2501–9.