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ORIGINAL RESEARCH

Heterogeneity of determining disease severity, clinical course and outcomes in systemic sclerosis-associated interstitial lung disease: a systematic literature review

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ABSTRACT

Objective The course of systemic sclerosis-associated interstitial lung disease (SSc-ILD) is highly variable and different from continuously progressive idiopathic pulmonary fibrosis (IPF). Most proposed definitions of progressive pulmonary fibrosis or SSc-ILD severity are based on the research data from patients with IPF and are not validated for patients with SSc-ILD. Our study aimed to gather the current evidence for severity, progression and outcomes of SSc-ILD.

Methods A systematic literature review to search for definitions of severity, progression and outcomes recorded for SSc-ILD was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in Medline, Embase, Web of Science and Cochrane Library up to 1 August 2023.

Results A total of 9054 papers were reviewed and 342 were finally included. The most frequent tools used for the definition of SSc-ILD progression and severity were combined changes of carbon monoxide diffusing capacity (DLCO) and forced vital capacity (FVC), isolated FVC or DLCO changes, high-resolution CT (HRCT) extension and composite algorithms including pulmonary function test, clinical signs and HRCT data. Mortality was the most frequently reported long-term event, both from all causes or ILD related.

Conclusions The studies presenting definitions of SSc-ILD 'progression', 'severity' and 'outcome' show a large heterogeneity. These results emphasise the need for developing a standardised, consensus definition of severe SSc-ILD, to link a disease specific definition of progression as a surrogate outcome for clinical trials and clinical practice.

PROSPERO registration number CRD42022379254.Cite Now

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Progression of interstitial lung disease (ILD) is associated with the poorer outcome in systemic sclerosis (SSc).
⇒ Established and validated criteria of progressive and severe SSc-ILD are required to drive monitoring and intensification of treatment strategy.
⇒ Most proposed definitions are derived from idiopathic pulmonary fibrosis and are not fully validated for patients with SSc-ILD.

WHAT THIS STUDY ADDS

⇒ This systematic literature review summaries the current data of different definitions used in clinical trials and observational studies.
⇒ The large heterogeneity of presented definitions emphasises the need to develop standardised, consensus definitions.
⇒ Patients' perspective need also to be taken into account, in particular when defining disease-related outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The definition of progression should be the surrogate outcome for long-term severe events, meaningful for both patients and physicians.
⇒ Our data are the basis to create a disease-specific definition of progression of SSc-associated interstitial lung disease.
⇒ This will further allow the identification of a patient phenotype at higher risk of progression, as possible candidate for treatment intensification.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by tissue inflammation and vasculopathy, leading to skin and internal

organs fibrosis.[1 2] Mortality related to SSc is the highest among all rheumatic diseases,[3] and the 10-year survival rate of patients with SSc is 65%–73% in Europe and 54%–82% in North America.[4] Interstitial lung disease (ILD) is a prominent feature of SSc and is the leading cause of death according to 'European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) cohort data.[3 5] Nearly 50% of patients with SSc develop ILD during the disease course, with the higher risk in early phases, in particular for the diffuse cutaneous subset (dcSSc).[6 7] Although the high-resolution CT (HRCT) of the chest is the gold standard imaging technique for ILD assessment, pulmonary function tests (PFTs) and clinical assessment of respiratory symptoms also play a significant role in the management of patients with SSc-ILD. Half of the patients with SSc have confirmed ILD on first chest HRCT assessment.[8] Restrictive patterns on PFTs with reduced forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) are detected more rarely.[9]

At SSc diagnosis, screening for ILD is recommended in every patient with SSc based on expert evidence-based European and American consensus documents.[10 11] Despite this, still too many physicians tend to perform diagnostic HRCTs only when patients develop respiratory symptoms or to screen only in patients at higher risk (eg, dcSSc, positive for Scl-70 antibodies, African-American ethnicity, high modified Rodnan skin score (mRSS)).[12–17]

Compared with the progressive fibrosing disease course of idiopathic pulmonary fibrosis (IPF), the course of SSc-ILD may be highly heterogeneous,[18] with stable and progressive periods. A recent EUSTAR database analysis showed that 67% of all patients with SSc-ILD may experience progression at any time over an average follow-up of 5 years, with most patients with progressive ILD showing a rather slow lung function deterioration afterwards or even no episode of further major decline.[19]

Currently, no established consensus is available on the definition of SSc-ILD progression among experts and in the literature. In observational studies and clinical trials, the most used definition of ILD progression is a ≥10% relative decline in FVC.[20–29] An FVC relative decline ≥10% is a strong predictor of reduced survival in patients with SSc-ILD.[29] Some studies prefer to use the CT fibrosis extent as a marker of ILD progression.[30–32] The recent 2022 American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Thoracic Association (ALAT) Clinical Practice Guideline on Progressive Fibrosing ILDs defined progressive pulmonary fibrosis on the basis of the presence of at least two of the following three criteria occurring within 1 year: worsening respiratory symptoms, physiological evidence of disease progression (absolute decline in FVC of at least 5% predicted or/and absolute decline in DLCO at least 10% predicted) and radiological evidence of disease progression.[33] Taking into account differences between SSc-ILD and IPF, post-hoc analysis of the Scleroderma Lung Study (SLS) I and II indicated a decline in FVC of 3.0% as the minimal change for a clinically important difference.[34]

The objective of this systematic literature review (SLR) is to collect the available scientific evidence about definitions of severity, progression and outcomes in SSc-ILD. The final aim is to inform the creation process of the definition of 'long-term severe SSc-ILD'. This long-term outcome will then be linked to a definition of ILD progression specific for SSc, as surrogate outcome, to help guiding decisions for management and monitoring disease course for patients diagnosed with SSc-ILD.

MATERIALS AND METHODS

A systematic search of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify papers that include definitions of SSc-ILD severity, progression and outcome (PROSPERO registration number CRD42022379254). We considered outcomes as events that were recorded during a study and had impact on the patients' health and could be related to ILD. These were different from measurements and definitions of progression, which was only related to ILD and therefore recorded separately.

In summary, Medline, Embase, Web of Science databases and Cochrane Library were searched up to 1 August 2023. A single author (CB) with established experience[35–37] performed the literature search using the search, strings detailed in online supplemental file 1.

The citations retrieved from these databases were entered in the software EndNote V.20 and duplicates were removed. The citations were evaluated in a two-step process by teams of two independent evaluators (LP, FB, CC, EF, SP, ST, PB, CC, RDL, AE, JL), including title/abstract evaluation (step 1) and full-text evaluation (step 2). Discrepancies were resolved by direct discussion between the two assessors, otherwise through the opinion of a third evaluator (CB). Randomised clinical trials (RCT), cross sectional or longitudinal studies (both retrospective or prospective) were included in the SLR if they were focused on SSc or on cohorts in which data on patients with SSc could be extracted, considered ILD as primary target (representing at least one of population, exposure, outcome) and included at least 10 adult patients. Exclusion criteria were papers written in languages other than English, non-clinical studies, lung involvement due to other causes (ie, other diseases, smoking or professional exposure, etc), ILD onset as an outcome, literature reviews and no full-text availability.

A reproducibility exercise was conducted on the first 20 abstracts for step 1 and the first 5 full texts for step 2 derived from the selection and performed by all extractors, to ensure homogeneity in evaluation and data extraction (90% of agreement achieved).

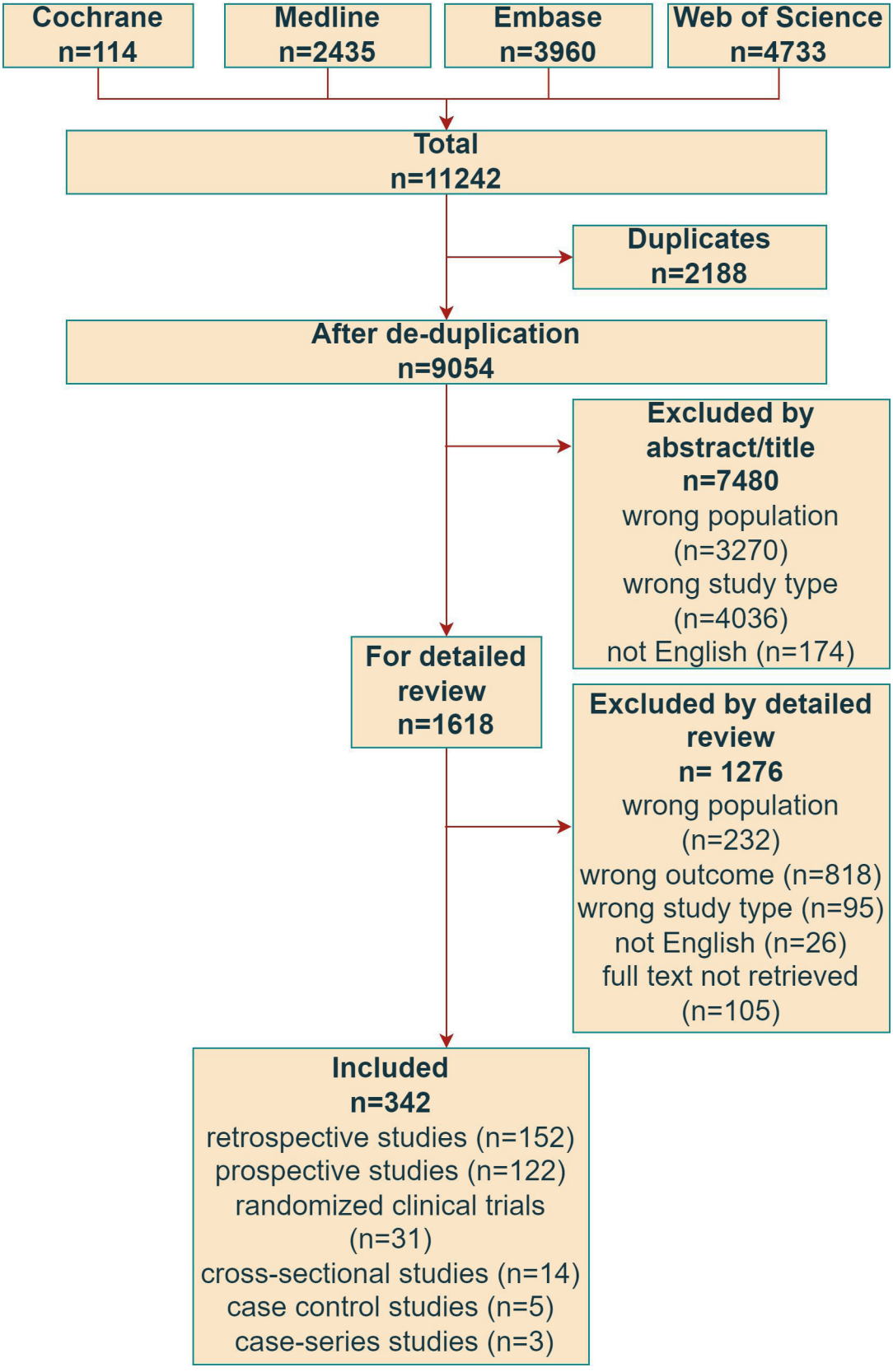

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of studies selection. ILD, interstitial lung disease; SSc, systemic sclerosis.

RESULTS

Out of 9054 papers identified by the primary literature search, 1618 articles were selected for full-text analysis (figure 1). The reasons for exclusion from the first selection step were: wrong population (n=3270), wrong study type (n=4036) and not English article (n=174). Among the remaining 1618 papers evaluated as full text in step 2, 1276 manuscripts were excluded due to no definition of severity/progression/outcome presented (n=818), wrong population (n=232), wrong study type (n=95), full texts not retrieved (n=103) and not English paper (n=26). Finally, 342 manuscripts were extracted in step 3, including 43 939 patients with SSc-ILD, range 6–3778 patients per paper (data available for 305/342 papers). Mean age was 50 years and ranged from 32 to 66 years (data available for 141/342 papers), the median age ranged from 18 to 75 years (data available for 29 papers), 68.6% were women (data available for 161/342 papers). The mean disease duration ranged from 1 to 11 years (data available for 165/342 papers). The design of the study was retrospective in 167 cases (49%), prospective in 122 (37%), RCT in 31 (9%), cross-sectional in 14 (4%), case control in 5 (1%) and case-series in 3 (0.9%). Regarding the SSc classification criteria, 147 studies used the 2013 American College of Rheumatology (ACR)/EULAR criteria, 125 the 1980 ARA criteria, in 20 studies patients meet 2013 ACR/EULAR criteria and 1980 ARA criteria simultaneously, 7 papers used other criteria (including Leroy and others) and 43 did not indicate any criteria.

The SLR results are summarised below and divided in three sections: definitions of severity, progression and outcomes of SSc-ILD.

Definitions of SSc-ILD severity

A definition of SSc-ILD severity was included in 155 (45%) papers. It was based on HRCT data in 62 (40%) studies, on combined HRCT and FVC changes in 25 (16%), on FVC changes in 27 (17%), on combined FVC and DLCO changes in 15 (10%) and on DLCO changes in 12 (8%). The most used definitions of SSc-ILD severity are given in table 1, and less frequent are mentioned in online supplemental table 1.

ILD extent presented as percentage of affected parenchyma on HRCT was the most frequently used imaging parameter (89 studies, 8327 patients), both alone (62 studies, 4974 patients) or in combination with PFT parameters (27 papers, 3353 patients). Different cut-off points were proposed, ranging from >10% to >50%: the most frequent cutoff was >20% as proposed by the visual Goh *et al* staging system on five levels,[38] which was presented in 24 studies including 2031 patients. According to the modified Goh *et al* scoring system, extensive disease was defined as lung involvement>20% on HRCT or 10%–30% ILD involvement on HRCT with FVC<70% predicted. Limited disease was determined as ≤20% ILD involvement on HRCT or 10%–30% lung involvement on HRCT and an FVC≥70% predicted.[38]

The second most frequently used HRCT assessment tool of ILD severity was the semiquantitative scoring proposed by Warrick *et al*,[39] which combines severity and extent of disease. In this score, different abnormalities (ground-glass opacity alone, mixed ground glass and reticular disease, reticular fibrosis alone and honeycombing) correspond to increasingly severe disease and consequently receive increasingly higher scores. The extent is determined based on the total number of bronchopulmonary segments involved for each abnormality, with a maximum score of 31 points. The Warrick score was used in 10 studies, including altogether 519 patients with considered cut-off >15 points (in 3 studies), >10 points (in 1 study) and >7 (in 2 studies).

The other HRCT assessments to present ILD severity were the CT score grade 3 or grade 4 as corresponding to 50%–74% or >75% or lung parenchyma involved (five studies), the predominance of reticular or honeycombing appearance (four studies), extensive-ILD Z score≥3 (two studies), presence of ground glass opacities (one study), presence of linear opacities of >3 mm thickness and presence of honeycombing (one study).

PFTs parameters were used as assessment tools for SSc-ILD severity in 67/155 papers, including altogether 8766 patients (as part of combined indexes in 40 studies) with % predicted FVC as the most frequently used parameter. FVC was used to define severity as a single parameter in 27 papers (5078 patients), in combination with % predicted DLCO in 15 papers (1519 patients) or with other parameters in 25 papers (3287 patients). Among the included studies, a cutoff for FVC<45% was used in 1 paper (246 patients), FVC<50% was used in 27 papers (4026 patients), <60% in 1 paper (20 patients), <70% in 29 papers (5298 patients) and<80% in 2 paper (3867 patients). Per cent predicted DLCO as isolated severity marker of SSc-ILD was presented in 12 studies including 588 patients, with a cutoff <40% (4 papers, 117 patients), <50% (4 papers, 315 patients) or <70% (4 papers, 156 patients).

There were some composite measures for ILD severity in the literature: the ILD—Gender, Age, Physiology index (taking into account the ILD subtype, gender, age, FVC and DLCO), a composed index (including the body mass index, DLCO results, Medical Research Council dyspnoea score (mMRC) and the 6-min walking distance (6MWD)), and the du Bois index. The Medsger severity scale was used in three studies including altogether 63 patients.

The severity of ILD was estimated also according to the clinical symptoms: exercise tolerance/dyspnoea score>1 (1 paper, 57 patients), NYHA functional class III-IV (1 paper, 21 patients), exercise oxygen desaturation (1 paper, 63 patients) and a grade IV on the mMRC (1 paper, 28 patients).

Definitions of SSc-ILD progression

Out of 207 studies including definitions of SSc-ILD progression, 62 (30%) provided a definition referred to

Table 1 Definitions of SSc-ILD severity

	SSc cohort, n articles	SSc cohort, n (from n of articles)	Among SSc cohort, n ILD (from n of articles)	Severe ILD in SSc cohort, n (%) (from n of articles)	References	SSc-ILD cohort, n articles	SSc-ILD cohort, n patients (from n of articles)	Severe ILD in SSc-ILD cohort, n patients, (%) (from n of articles)	References
PFTs									
FVC<50%	11	4148 (11)	2318 (10)	195 (22%) (9)	63–72	3	209 (3)	11 (7%) (2)	73–75
FVC<70%	9	6164 (9)	2151 (7)	1716 (30%)	76–84	2	65 (2)	37 (60%) (2)	85 86
DLCO<40%	3	231 (3)	98 (3)	39 (43%) (2)	87–89	1	19	–	90
DLCO<50%	4	1021 (4)	315 (4)	175 (16) (4)	67 84 91 92				
DLCO<70%	4	270[1]	156 (1)	84 (36%) (1)	85 91 93				
DLCO<50% and/or FVC<50%	12	4159 (12)	1071 (9)	164 (30) (5)	94–105				
HRCT									
ILD extent>10%	4	1099 (4)	478 (3)	104 (24%) (3)	8 106–108	1	14 (1)	8 (57) (1)	109
ILD extent>20%	12	2255 (12)	960 (10)	380 (36%) (10)	9 30 110–119	12	1071 (12)	271 (44%) (10)	29 61 120–129
ILD extent>30%	3	2706 (3)	779 (3)	90 (14%) (2)	107 130				
ILD extent>50%	2	111 (2)	82 (2)	8 (14%) (1)	131 132	2	144 (4)	–	133 134
Warrick ILD score>15 points	3	234 (3)	171 (3)	29 (28%) (2)	98 135 136				
Warrick score	2	101 (2)	61 (2)	4 (44%) (1)	137 138	3	173 (2)	8 (57.1%) (1)	139–141
According to HRCT score, grade 3 as 50–74% and grade 4 as>75%						5	359 (5)	16 (6.5%) (2)	142–146
Combined measurement									
ILD>20% and FVC<70%	2	770 (2)	273 (2)	51 (33%) (2)	147 148	7	709 (7)	230 (36%) (6)	122 149–154
ILD extent>30% or ILD extent 10–30% with FVC<70%	6	876 (6)	374 (5)	177 (37%) (5)	155–160	6	1103 (5)	139 (42%) (4)	161–166

DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; PFTs, pulmonary function tests.

combined DLCO and FVC changes, 65 (31%) to isolated FVC changes, 27 (13%) to DLCO changes, 20 (10%) to HRCT extension, 13 (6%) to combination of PFT and HRCT data, 11 (5%) to combination of PFTs, clinical signs and HRCT data, 5 (2%) to vital capacity decline and 4 (2%) to other aspects (tables 2 and 3). The time frame of progression assessment were 6 months (5.3% papers), 12 months (35.3 %), 24 months (18.4% papers), 36 months (7.7%), 60 months (3.4%), more than 60 months (7.7%), other (9.2 %) or unknown (13.0%).

Among PFTs parameters, FVC was the most frequently used in 150/207 manuscripts. Among the included manuscripts, various cutoffs for decline were presented, representing FVC decline over a variable follow-up duration (tables 2 and 3 and Supplement table 2,3): >20% in 3 papers (96 patients), >15% in 6 papers (390 patients), >10% in 108 papers (14 237 patients), 5%–10% 13 papers (1656 patients), >5% in 14 papers (2075 patients), >3.3% in 4 papers (1418 patients), > 0.08 L per year in 1 paper (29 patients), any decline in 1 paper (148 patients). In addition, progression to FVC<70% at 36 months was recorded in 2 papers (212 patients) and <55% at follow-up in another paper (44 patients). Percent decline of DLCO as marker of SSc-ILD progression was presented in 103 studies including 10 152 patients. Also for DLCO decline, different cutoffs have been proposed over different time points (tables 2 and 3 and Supplement table 2,3): >30% (1 paper, 34 patients), >20% (2 papers, 53 patients), >15% (69 papers, 8766 patients), >10% (26 papers, 1152 patients), >7% (1 paper, 33 patients), >5% (1 paper, 25 patients), DLCO<70% at longest follow-up (1 paper, 44 patients) and any decline in 1 paper (44 patients).

The most frequently used definition of SSc-ILD progression based on PFT changes were decline FVC>10% or 5%–10% plus DLCO>15% (53 studies, 7553 patients), otherwise as decline FVC>10% or DLCO>10% (14 studies, 825 patients).

Definitions based on HRCT changes included the increase of ILD extent by >5% in 2 paper (102 patients), >10% in 4 papers (358 patients), >20% in 6 papers (308 patients), ≥2% increase in quantitative ILD score[40] in 2 papers (269 patients), ≥4% increase in quantitative ILD score[40] in 1 paper (97 patients), increase in the ILD score proposed by Kazerooni *et al*[41] ≥ 1 point in 1 paper (73 patients) or ≥2 points in 2 papers (116 patients), otherwise any increase in ILD extent in 6 papers (697 patients). The Kazerooni assessment strategy includes the extent of ground-glass opacity (alveolar score) and honeycombing (interstitial score) on a scale of 0–5 in the three lobes of both lungs as follows: 0—no alveolar disease, 1—ground glass involving <5% of the lobe, 2—ground glass involving up to 25% of the lobe, 3—ground glass involving 25%–49% of the lobe, 4—ground glass involving 50%–75% of the lobe, 5—ground glass involving >75% of the lobe for alveolar score; 0—no interstitial disease, 1—septal thickening without honeycombing, 2—honeycombing involving up to 25% of the lobe, 3—honeycombing involving 25%–49% of the lobe, 4—honeycombing involving 50%–75% of the lobe, 5—honeycombing involving >75% of the lobe for interstitial score.[41] The increasing extent ILD was also part of a composite definition in 9 papers (1196 patients), combined with decline FVC and/or DLCO with deterioration of dyspnoea symptoms.

Finally, progression of ILD was also estimated according to clinical symptoms in 11 papers (944 patients), all using worsening of dyspnoea in combination with PFT or HRCT changes.

Complementary to ILD progression, 16/342 papers presented definitions of SSc-ILD improvement. Generally, the most frequently used definitions were based on PFTs changes: isolate increase of FVC (7 studies, 262 patients) with cutoff of 3.6%, 5%, 10% or 15% (Supplementary Table 4), isolate increase DLCO (2 studies, 45 patients) with cutoff of 10% and 15%, increase FVC or DLCO (5 studies, 123 patients), improvement in VC>10% (1 study, 7 patients) and increase 6MWD>15% (1 study, 7 patients).

Definitions of SSc-ILD outcome

The last part of our study was focused on outcomes in SSc-ILD. Information about outcomes of SSc-ILD was present in 175 articles. The most frequent endpoint was mortality (table 4). According to the SRL results, mortality was categorised to mortality due to ILD (12 studies, 2628 patients), SSc-related mortality (8 studies, 2091 patients), 15-year mortality (2 studies, 628 patients), 10-year mortality (16 studies, 2732 patients), 5-year mortality (22 studies, 4771 patients), 3-year mortality (10 studies, 952 patients), 1-year mortality (13 studies, 947 patients), in-hospital mortality (5 studies, 1899 patients), mortality after lung transplantation (1 study, 72 patients) and overall mortality with follow-up duration from 12 months to 360 months (68 studies, 8076 patients). Other popular recorded outcomes of patients with SSc-ILD were hospitalisation (6 papers, 1835 patients), end-stage ILD (6 paper, 501 patients), lung transplantation (3 papers, 375 patients) and infections (2 papers, 82 patients).

Parameters of other SSc-related organ progressions or improvement were also considered as outcomes in 21/175 studies (Supplementary Table 5), such as malignancy, changes in the mRSS, left ventricular ejection fraction, new onset of pulmonary hypertension, new onset of digital ulcers, overall disease progression (defined according to the occurrence of at least one organ progression), compression fractures, femoral head necrosis, newly diagnosed arterial hypertension, newly diagnosed diabetes, hyperlipidaemia requiring treatment, abnormal liver function tests and decrease Health Assessment Questionnaire Disability Index. The duration of patients' follow-up for outcome assessment ranged from 1 to 30 years.

Table 2 Definitions of SSc-ILD progression based on a single parameter

	SSc mixed cohorts					SSc-ILD cohorts			
	Time, months (n papers)	n patients (n papers)	n ILD patients (n papers)	n progressors (n papers)	References	Time frame, months (n papers)	n patients (n papers)	n progressors (n papers)	References
FVC									
Decline FVC>15%	6 (1) 65 (1)	200 (2)	84 (2)	19 (2)	167 168	12 (2) 60 (1)	253 (3)	26 (3)	29 169 170
Decline FVC>10%	12 (9) 24 (4) 36 (4) 48 (1) >60 (3) Unk (3)	11 604 (22)	2746 (20)	976 (19)	20–27 30 71 116 171–179	6 (3) 12 (5) 24 (6) >60 (4)	3007 (18)	424 (16)	28 29 74 75 125 150 161 180–190
Decline FVC>5%	12 (1) Unk (1)	6527 (2)	100 (1)	401 (2)	191 192	12 (4) 24 (3) Unk (1)	1777 (8)	589 (6)	28 124 188 189 193–196
Decline FVC>3.3%	–	–	–	–	–	12 (1) 48 (1) 52 (1) Unk (1)	1418 (4)	571 (3)	197–200
DLCO									
Decline DLCO>15%	12 (2) 24 (1) 60 (2)	568 (5)	445 (5)	135 (5)	24 118 172 173 191	6 (2) 12 (2) 36 (1) 60 (2)	505 (7)	168 (7)	29 85 161 170 183 201 202
Decline DLCO>10%	12 (2) 55 (1) >60 (1) Unk (1)	340 (5)	112 (2)	86 (5)	167 171 176 203 204	24 (2)	30 (2)	9 (1)	140 195
HRCT									
Increase ILD extent>10%	12 (2)	347 (2)	213 (2)	6 (2)	30 205	24 (2)	145 (2)	5 (2)	31 32
Increased ILD extent>20%						24 (1) Unk (1)	22 (2)	8 (2)	206 207
Increase ILD extent	12 (1) 24 (1) 37 (1) 62 (1)	1103 (4)	480 (4)	105 (4)	148 208–210	12 (1) 24 (1)	217 (2)	34 (1)	211 212

DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease.

Table 3 Definitions of SSc-ILD progression based on the combination of multiple parameters

	SSc mixed cohorts					SSc-ILD cohorts			
	Time, months (n papers)	n patients (n papers)	n ILD patients (n papers)	n progressors (n papers)	References	Time frame, months (n papers)	n patients (n papers)	n progressors (n papers)	References
PFTs									
Decline FVC>10% or DLCO>15%	6 (1) 12 (6) 24 (3) >36 (5) >60 (1) Unk (6)	10476 (18)	4258 (14)	1144 (14)	8 70 116 117 148 208 213–225	6 (1) 12 (9) 24 (4) 36 (1) >60 (3) Unk (8)	1571 (22)	461 (18)	32 38 123 152 153 226–241
Decline FVC>10% or DLCO>10%	6 (1) 12 (2) >36 (4) 60 (1)	531 (8)	336 (8)	181 (8)	174 205 242–245	12 (1) 24 (1) 36 (2) >36 (2)	489 (6)	47 (4)	121 246–250
Decline FVC>10% and/or decline FVC 5%–9% with decline DLCO>15%	6 (1) 12 (2) 24 (1)	878 (4)	495 (4)	110 (4)	251–254	12 (2) Unk (1)	772 (3)	96 (1)	154 192 255
PFTs+HRCT									
Decline FVC≥10% or DLCO≥15% or ILD extent increase>20%	12 (1) 21 (1) 24 (1)	462 (3)	204 (3)	55 (3)	113 256 257	12 (1) 56 (1)	72 (2)	15 (2)	258
PFTs or HRCT+clinical signs									
Decline FVC>10% or decline FVC 5%–10% and worsening f respiratory symptoms or/and increase ILD extent	24 (1)	36 (1)	22 (1)	9 (1)	259	12 (1) 36 (1) Unk (1)	109 (3)	48 (1)	260–262

DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease.

Table 4 Definitions of outcome in SSc-ILD

	SSc mixed cohorts					SSc-ILD cohorts			
	Time, months (n papers)	n patients (n papers)	n ILD patients (n papers)	n of patients with outcome (n papers)	References	Time, months (n papers)	n patients (n papers)	n of patients with outcome (n papers)	References
Mortality due to ILD	180 (12)	6165 (12)	2628 (10)	277 (12)	23 24 65 118 138 167 263–267	–	–	–	–
SSc-related mortality	25-200 (7) UNK (1)	3789 (7)	1785 (7)	324 (7)	23 65 264 266 268 269	97 (1)	306 (1)	39 (1)	17
15-year mortality	–	1284 (1)	522 (1)	260 (1)	270	–	106 (1)	21 (1)	154
10-year mortality	–	7484 (13)	2509 (10)	1991 (13)	23 78 106 111 130 179 214 267 268 271–273	–	223 (3)	46 (3)	144 150 274
5-year mortality	–	10 604 (16)	4335 (15)	1104 (13)	23 84 106 111 173 225 242 267 268 271–273 275–277	–	436 (6)	117 (6)	274 278–282
3-year mortality	–	1046 (5)	688 (5)	134 (5)	158 173 242 268 275	–	264 (5)	25 (5)	127 152 279 281 283
1-year mortality	–	1153 (5)	633 (5)	33 (2)	254 268 272 273 275	–	314 (8)	12 (6)	280–287
Mortality	12–360[36]	23 366 (35)	5048 (26)	2338 (31)	5 8 23 25 64–66 92 114 117–119 131 147 160 174 177 219 244 266–268 288–300	12–348 (32)	3028 (31)	582 (27)	17 28 50 71 85 128 141 142 149 151 153 163 170 185 226 238 242 258 269 274 278 301–311
In-hospital mortality	120 (1) 12 (1) Unk (3)	14 240 (4)	1899 (3)	164 (3)	312–316	–	–	–	–
Mortality after lung transplantation						45–72[1]	72 (1)	27 (1)	317
Hospitalisation	12 (1) 120 (2) 84 (1) Unk (3)	6211 (5)	1261 (4)	591 (4)	312 314 316 318 319	12 (1)	574 (1)	78 (1)	166
End-stage ILD	12 (1) 60 (1) 120 (1) 200 (2)	1646 (5)	451 (4)	111 (5)	65 245 320–322	173 (1)	50 (1)	16 (1)	323
Lung transplantation	120 (1) 200 (1)	552 (2)	203 (2)	17 (2)	65 179	60 (1)	172 (1)	3 (1)	301
Infections	120 (1)	95 (1)	36 (1)	26 (1)	312	120 (1)	46 (1)	9 (1)	144

ILD, interstitial lung disease; SSc, systemic sclerosis; Unk, unknown/not specified.

DISCUSSION

In more than a half of the patients with SSc, ILD may determine a meaningful impact on quality of life, morbidity and survival.[5 7] Unlike the progressive fibrosing disease course of IPF, the course of SSc-ILD is definitely variable, with phases of rapid or slow disease progression, disease stability or improvement.[19] In fact, ILD progression can be observed not only during the first 3 years of disease duration, but also in later stages. In patients with SSc, a recent analysis from the EUSTAR cohort showed that the frequency of ILD progression is over 10% every year, regardless of disease duration, which ranged from less than 3 to more than 15 years after onset of Raynaud's phenomenon.[42] The high heterogeneity of the course of SSc-ILD requires appropriate monitoring and approach to treatment strategy.

Although there is no consensus on which definition of SSc-ILD progression best fits the case of a surrogate outcomes, most ILD progression definitions have been related to increased morbidity and mortality. This stresses the need to identify patients at higher risk of progression, to start an early treatment.[43] Overall, there is consensus among SSc-ILD experts that the definition of SSc-ILD progression should cover multiple domain that are usually affected by this complication.[44] The recent 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline on progressive fibrosing ILD based the definition of ILD progression on at least two of worsening of respiratory symptoms, physiological evidence of disease progression and radiological progression, presenting within a 1–2 years' time frame.[33] Despite being currently proposed to define a progressive phenotype also in SSc, the current definition has not been tested so far in this disease, and therefore lacks a data-driven support. Similarly, the "Efficacy and safety of Nintedanib in patients with progressive fibrosing interstitial lung disease" (INBUILD) study defined a progressive ILD phenotype as a relative decline in the FVC predicted≥10% or a relative decline in FVC predicted of 5%–10% associated to worsening of respiratory symptoms or an increased extent of fibrosis on HRCT, or worsening of respiratory symptoms. These events could be recorded over a time observation up to 24 months and manifest despite management with standard of care treatments, excluding nintedanib or pirfenidone.[45] However, only a small proportion of SSc-ILD cases were included in this study, which limits the possibility to extrapolate the applicability of this definition to this specific population.

Applying a combined and multidomain definition of progression in the large prospective Canadian Registry for Pulmonary Fibrosis, progression events were recorded in in 49% patients with SSc-ILD within 24 months. Progressive fibrosing-ILD (PF-ILD) was defined as a relative FVC decline ⩾10%, death, lung transplantation or any two of: relative FVC decline ⩾5% and<10%, worsening respiratory symptoms or worsening fibrosis on CT of the chest, all within 24 months from baseline. Based on which definition was used to determine progression, the frequency of events ranged from 8% (relative FVC decline 5%–9% with fibrosis on CT) to 49% (relative FVC decline ⩾10%).[46] However, it should be highlighted that pulmonology registry are likely enriched for progressive, severe patients and reflects daily practice in pulmonology, which is not necessarily representative of the daily clinical practice in rheumatology. Although based only on functional decline, the number of progressive events in EUSTAR cohort are, in fact, much lower.[19] A study from a large European centre by Nasser *et al* reported that 168 out of 617 patients (27%) met the PF-ILD criteria during a 7-year period.[47] Another retrospective study including nine specialist centres in the UK by Simpson *et al* identified the new incident cases of PF-ILD rate according to the INBUILD criteria in 14.5% assessed over a 2-year period.[48] Finally, another recent analysis of 826 patients with SSc-ILD from the EUSTAR database showed that 27% patients experienced ILD progression defined as a decline in predicted FVC>5% during any 12-month period, and 67% of all patients with SSc-ILD experienced progression at any time over the mean 5-year follow-up.[19] However, most patients with SSc-ILD (58%) were stable (decline or increase in FVC<5%) or improved (increase in FVC≥5% predicted) during any 12-month period and only 8% showed rapid, continuously declining FVC.[19]

Our SLR focuses on definitions of severity, progression and outcome for patients with SSc-ILD, considering the existing literature data until 1 August 2023. As a result of our research, we presented data on 175 articles regarding the SSc-ILD outcomes. The most frequent outcomes were mortality (157 studies), end-stage lung disease (6 studies) and hospitalisation (6 studies). Concerning severity of SSc-ILD, ILD extent on HRCT over 20% of the parenchyma is most frequently used, alone or in combination with PFT parameters. Among PFTs parameters for severity assessment, predicted FVC values <50% or <70% and predicted DLCO values <40%, <50% or <70% were used in most papers. Our review also confirmed the importance of both PFTs (mostly using FVC% predicted and DLCO% predicted), and HRCT as a tool to identify progressive SSc-ILD. Finally, several studies have proposed criteria for progression of SSc-ILD based on a combination of clinical signs (worsening of dyspnoea) in combination with pulmonary function measures and radiographic extent of fibrosis on HRCT.

Independent of the definition used, it is important to detect ILD progression, as it can represent a surrogate outcome for future severe events.[49] Using data from the SLS I and II, the post-hoc analysis by Volkmann *et al* demonstrated that radiographic progression of SSc-ILD (defined by a≥2% increase in total quantitative ILD score—QILD score) over the course of 1–2 years is associated with an increased risk of long-term mortality.[50] Even after adjusting for other factors known to affect survival in patients with SSc, worsening of ILD on HRCT remained associated with mortality, in particular in the SLS II subgroup.[50] The ability of PFT changes at 1 and 2 years to predict long-term mortality over more than 15

years was estimated in study by Goh *et al*.[29] The changes in the FVC% predicted in 1 year provided the most accurate prognostic information, with the optimal expression of FVC change consisting of either a ≥10% decline in the FVC from baseline or a 5%–9% decline in the FVC with a ≥15% decline in the DLCO. The prognostic value of PFT trends in the whole cohort was entirely explained by the disease progression in patients with extensive lung fibrosis, defined as ILD affecting more than 20% of the lung parenchyma. The categorical changes in the carbon monoxide transfer coefficient (KCO) and the FVC:DLCO ratio in those with limited lung fibrosis and change in the composite categorical decline (a≥10% decline in the FVC from baseline or a 5%–9% decline in the FVC with a ≥15% decline in the DLCO) in those with extensive lung fibrosis at 2 years were independent prediction factors of mortality. The prognostic value of the PFT changes was further confirmed in a mortality prediction model using data from the SLS I and II trials.[17] The final SLS II survival models demonstrated that older age, higher baseline values of modified Rodnan's skin score, as well as a more meaningful decline of FVC%-predicted and DLCO%-predicted over 24 months were associated with worse survival. Despite the established value of PFT as a surrogate marker of mortality in SSc-ILD, the EUSTAR study by Hoffmann-Vold AM *et al* could not identify significant differences in mortality between patients with a≥10% decline in the FVC (12%), decline in FVC 5%–10% predicted (15%) or decline or increase in FVC<5% (9%) over the initial 12-month period.[19]

Severe disease and long-term outcomes are the cornerstone of SSc-ILD management, as they represent the target that should be avoided or delayed through medications. The currently available RCTs on SSc-ILD used FVC decline as an outcome due to its good surrogacy for survival [SLS I—percentage of the predicted FVC value at 12 months, SLS II—percentage of the predicted FVC value at 24 months, the "Safety and Efficacy of Nintedanib in Systemic Sclerosis" (SENSCIS) study —the annual rate of absolute decline in FVC assessed over 52 weeks, FaSScinate and FocuSSced trial—percentage of the predicted FVC value at 48 weeks).[26 28 51–53] In comparison to SSc-ILD, the field of RCTs in PAH has moved forward from using pure functional outcomes as primary endpoints, aiming at preventing morbidity and mortality events. For example, the primary outcome in the "study with an ERA in Pulmonary arterial Hypertension to Improve cliNical outcome" (SERAPHIN) trial was the time from the initiation of treatment to the first occurrence of a composite end point of death, or worsening of pulmonary arterial hypertension (defined as events such as atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids).[54] Similarly, the "study of first-line Ambrisentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertension" (AMBITION) trial used the first event of clinical failure as primary endpoint, which was defined as the first occurrence among death, hospitalisation for worsening pulmonary arterial hypertension, disease progression or unsatisfactory long-term clinical response.[55] Therefore, the combination of long-term outcomes and severe disease worsening, including both functional, radiological and clinical events, could help to create a combined morbidity–mortality outcome also for SSc-ILD. This might be used as a primary endpoint in SSc-ILD trials, further supporting the beneficial long-term effects of currently used medications. In addition, a long-term severe outcome endpoint may also support the creation of a data-driven, SSc-specific definition of ILD progression, which could then represent a solid short-term surrogate outcome and allow the identification of patients at higher risk of progression.

Risk stratification is another successful achievement in PAH, allowing the identification of patients who should then be treated more aggressively and followed up more tightly.[56] In line with lack of agreed long-term outcomes and progression definitions, preliminary data are also available for risk risk strafication of SSc-ILD. Data from a post hoc analysis of the patients with SSc-ILD receiving placebo in the SENSCIS trial identified a modest association between larger extent of fibrotic ILD at baseline and a greater decline in FVC % predicted at week 52.[57] Conversely, a post hoc analysis of the FocuSSced trial did not show the significant differences in FVC% declining in placebo group based on QILD severity, possibly related to the different outcome (decline in absolute vs % predicted FVC) and the different inclusion criteria.[58] The prognostic value of higher FVC % predicted at baseline as a factor determining a higher risk of a decline in FVC>10% predicted over the next 12 months was also confirmed in recent analysis of patients with SSc-ILD in the EUSTAR database.[19]

In addition to pulmonary and other ILD features, other SSc-related extrapulmonary characteristics have shown association with ILD progression. In the same EUSTAR analysis, Hoffmann-Vold *et al* identified male sex, presence of reflux/dysphagia symptoms and high baseline mRSS as the strongest independent predictors of 5-year FVC decline, with significant interaction effects between time and these variables.[19] The association between oesophageal symptoms severity, even in the presence of PPI therapy, and future radiographic ILD progression was also confirmed in post analysis of SLS II study.[59] In addition to oesophageal features, early disease duration (<18 months since first non-Raynaud symptom), elevated inflammatory markers or extensive skin fibrosis (with mRSS≥18) at baseline have been also confirmed as risk factors for significant FVC decline in both the FocuSSced and the Senscis RCTs[26 60] Finally, lower SpO_2 after 6MWT and arthritis ever were identified as independent predictors of SSc-ILD progression defined as a relative decrease in FVC % ≥15%, or FVC%≥10% combined with DLCO % ≥15% at 1-year follow-up.[61]

There are some limitations of this overview. First, this SLR included only articles with available full text and in English language; therefore, additional relevant studies

might have been missed. Second, if an article was not identified by title or abstract as highlighting severity, progression or outcomes in SSc-ILD, it may not be detected during the screening process. Additionally, SLR was conducted in the four major electronic databases, Medline, Embase, Web of Science databases Cochrane Library, while other sources were not included.

In summary, the large heterogeneity of definitions of SSc-ILD 'progression', 'severity' and 'outcome' emphasise the need for further studies to develop standardised, consensus definitions, in which also patients' perspective must be included.[62] The results of the present SLR may represent the basis for the development process to create a disease-specific model to define progression of SSc-ILD, anchored to a predetermined specific definition of severe SSc-ILD. Overall, this initiative will aim at a better understanding of the variability of the course of SSc-ILD, thus allowing an accurate stratification of patients with SSc-ILD, timely treatment initiation and development of treatments goals.[43]

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