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Clinical science

Systemic sclerosis associated interstitial lung disease: a conceptual framework for subclinical, clinical and progressive disease

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Abstract

Objectives: To establish a framework by which experts define disease subsets in systemic sclerosis associated interstitial lung disease (SSc-ILD).

Methods: A conceptual framework for subclinical, clinical and progressive ILD was provided to 83 experts, asking them to use the framework and classify actual SSc-ILD patients. Each patient profile was designed to be classified by at least four experts in terms of severity and risk of progression at baseline; progression was based on 1-year follow-up data. A consensus was reached if $\geq$75% of experts agreed. Experts provided information on which items were important in determining classification.

Results: Forty-four experts (53%) completed the survey. Consensus was achieved on the dimensions of severity (75%, 60 of 80 profiles), risk of progression (71%, 57 of 80 profiles) and progressive ILD (60%, 24 of 40 profiles). For profiles achieving consensus, most were classified as clinical ILD (92%), low risk (54%) and stable (71%). Severity and disease progression overlapped in terms of framework items that were most influential in classifying patients (forced vital capacity, extent of lung involvement on high resolution chest CT [HRCT]); risk of progression was influenced primarily by disease duration.

Conclusions: Using our proposed conceptual framework, international experts were able to achieve a consensus on classifying SSc-ILD patients along the dimensions of disease severity, risk of progression and progression over time. Experts rely on similar items when classifying disease severity and progression: a combination of spirometry and gas exchange and quantitative HRCT.

Keywords: systemic sclerosis interstitial lung disease, connective tissue disease interstitial lung disease, systemic sclerosis associated interstitial lung disease subsets

Rheumatology key messages

- We created a rubric characterizing systemic sclerosis associated interstitial lung disease (SSc-ILD) along disease severity, risk of progression and progression.
- Experts used this framework to classify real patients in terms of these dimensions.
- This framework is a foundation for future classification criteria of SSc-ILD subsets.

Introduction

SSc is an autoimmune disease characterized by the presence of serological autoantibodies, vascular dysfunction, and progressive fibrosis of skin and internal organs [1]. SSc-associated interstitial lung disease (SSc-ILD) has a significant impact on quality of life and healthcare costs [2–5], and portends the highest risk for mortality of all potential organ involvement [6, 7]. More than 50% of SSc patients in North America have SSc-ILD [8], but the disease impact is heterogeneous, varying in terms of severity and progression [9]. This heterogeneity of ILD has been well-described, with identified SSc-ILD subsets, or subpopulations that share a similar clinical trajectory [10, 11]. With the advent of two Food and Drug Administration (FDA)-approved medications for the treatment of SSc-ILD [12, 13], there is an increasing need to develop consensus definitions of the varying SSc-ILD subsets for appropriate patient stratification [14–16].

A conceptual framework is a cognitive schema that may be used to characterize SSc-ILD subsets along the dimensions of severity, risk of progression and progression, and highlight the important variables used to delineate these subsets. A shared conceptual framework forms the basis for classification criteria, which are used for cohort enrolment in clinical studies and serve to identify those patients most likely to benefit from treatment in clinical trials. In terms of treatment and the development of therapy algorithms, decisions to initiate or advance treatment are often based on a shared understanding of severity, likelihood of progression and progressive disease. Thus, the objectives of this research effort were two-fold: (i) to build a conceptual framework that allows experts to classify severity, risk of progression and progressive disease in SSc-ILD, and (ii) observe how well the international experts agree with one another when using that framework and to identify those items most important in determining their classification.

Methods

Proposed conceptual framework and iterative revisions

Thirty-nine experts (disciplines including pulmonology medicine [$n = 19$], rheumatology [$n = 13$] and thoracic radiology [$n = 7$]) evaluated a proposed conceptual framework delineating subclinical, clinical and progressive ILD. Experts were invited to propose modifications and revisions; details on this process are available in the Supplementary Material, available at *Rheumatology* online. An updated framework was disseminated back to the working group for final feedback and subsequently presented at a national meeting [17].

Development of patient profiles

Eighty patient profiles were developed from participants in the Scleroderma Lung Study-II [18] ($n = 53$) and ILD patients seen at the University of Michigan Scleroderma Program ($n = 27$). All patients included in this study met 2013 American College of Rheumatology/European League Against Rheumatism Criteria for Systemic Sclerosis ($n = 80$). Experts in rheumatology, pulmonary medicine and radiology, and selected members of the Outcomes Measures in Rheumatology (OMERACT) CTD-ILD Working Group [14] provided key domains to be included in profiles.

Profiles were formatted to create baseline profiles and baseline with follow-up information over the course of 1 year profiles (Supplementary Fig. S1, available at *Rheumatology* online). Information on cardiopulmonary exercise testing (e.g. 6-min walking distance) and presence or absence of pulmonary hypertension was not included in the patient profiles due to a lack of available data (these data were not included uniformly in the two cohorts). Disease progression, as it is defined here, refers to progression of SSc-ILD, not other manifestations of the disease.

Expert classification

We identified 83 international experts (pulmonologists, rheumatologists and thoracic radiologists). Surveys were sent to the experts via the Qualtrics Online Survey tool (www.qualtrics.com); each survey took an estimated 30 min to complete.

The data generated from this study came from experts who volunteered to participate, after providing electronic consent on the survey provided to them. Each participant was informed and aware of his/her options to participate or decline participation. None of the data generated in the study came from patient participation.

The survey contained an introduction with a rationale for their participation, the conceptual framework for SSc-ILD subsets, and a collection of five baseline patient profiles and five baseline with follow-up profiles. Each baseline profile was classified by the expert on two dimensions: disease severity and risk of progression; each profile with follow-up was classified on one dimension: progression. For baseline profiles, the expert faced a forced choice for each profile with three options for severity (subclinical ILD, clinical ILD and unable to determine) and risk of progression (low risk, high risk and unable to determine). For follow-up profiles, the expert chose between four options for progression (stable ILD, progressive ILD, improved ILD or unable to determine). After classification, experts were required to identify factors influential in their classification decision, with a rank order preference with the top rank being the most influential, as previously done for SSc response criteria [19].

Experts were randomly selected to one of eight groups, where a minimum of four and up to 10 experts received a set of 10 profiles (five baseline and five baseline with follow-up surveys). The survey distribution discontinued when 80 profiles were fully adjudicated. A set was considered fully adjudicated when a minimum of four experts assessed the same set of profiles, with at least one expert being a rheumatologist and one being a pulmonologist. Consensus was defined as a concordance of $\geq$75% on a classification (e.g. three of four experts classified the profile the same way).

Agreement within and between disciplines (e.g. pulmonologists and rheumatologists) was determined by calculating the kappa coefficient for inter-rater reliability. Patient profiles were sent out in groups and rated by different sets of pulmonologists and rheumatologists. To calculate the kappa statistics among pulmonologists and the corresponding confidence intervals we used the following method. We first calculated the mean of pair-wise Cohen's kappa statistics between all possible pairs of pulmonologists in each group. For example, for a group of profiles that was rated by three pulmonologists, we can derive the mean kappa statistics based on three pairwise kappa statistics. We then calculated agreement among pulmonologists as the average of mean kappa among all groups. We used a bootstrap method to calculate the 95%

confidence interval for the above kappa statistics. Kappa results were interpreted as follows: 0.01–0.20 as none, 0.21–0.39 as minimal, 0.40–0.59 as weak, 0.60–0.79 as moderate, 0.80–0.90 as strong, and above 0.91 as almost perfect agreement [20].

The χ^2 statistic was used for comparing distribution of categorical variables. *P*-values <0.05 were considered to be significant for all tests.

Results

Proposed conceptual framework

A preliminary proposed conceptual framework (Supplementary Table S1, available at *Rheumatology* online) was created after careful review of the existing literature. Our working definitions were based on literature focusing on disease severity, items that prognosticate outcome, assessment of disease impact and treatment recommendations.

Iteratively revised conceptual framework

Table 1 is an update of Supplementary Table S1, available at *Rheumatology* online and incorporates the proposed set of working definitions based on experts' feedback. Four key concepts are illustrated in this revised conceptual framework. First, subclinical ILD was revised to include only asymptomatic patients regarding ILD; several experts clarified that subclinical ILD should be defined by the absence of symptoms attributable to ILD and that absence of symptoms is not synonymous with absence of disease. All experts agreed that detecting respiratory symptoms in patients with ILD is challenging for several reasons (e.g. diminished exercise capacity due to advancing cutaneous, musculoskeletal or pulmonary disease precluding effort that elicits dyspnoea), as is differentiating dyspnoea (e.g. secondary to ILD *vs* pulmonary hypertension or both). Second, in the context of a defined connective tissue disease, such as SSc, the radiographic changes seen in SSc patients, even if asymptomatic, are not included in the definition of interstitial lung abnormalities (ILAs), as agreed by a recently published expert statement [21, 22]. Third, experts commented that management of the disease should not be yoked to the SSc-ILD subset. In our original conception, subclinical ILD did not require treatment, clinical ILD generally did require treatment, and progressive ILD required change, escalation or addition of new therapies. The rationale for removing language about treatment was that this is a matter for empirical discovery; the classification

Table 1. Revised conceptual framework

Clinical features	Subclinical SSc-ILD All variables should be met but there may be exceptions	Clinical SSc-ILD Must have ≥1 feature
Demographics Age, sex, race	N/A	N/A
SSc disease factors SSc cutaneous classification Disease duration ANA status SSc specific autoantibody Modified Rodnan Skin Score	N/A	N/A
Respiratory symptoms Mahler Dyspnoea Index and Transitional Index Leicester Cough Questionnaire Patient Global Assessment St George's Respiratory Questionnaire	None	Present
Spirometry with gas exchange Forced vital capacity (% predicted) Diffusion capacity of carbon monoxide (% predicted)	Normal-to-near normal	Deficits present
Desaturation on exercise Oxygen desaturation during 6-min walk test	Normal-to-near normal	Deficits present
Quantitative HRCT Whole lung involvement (% of ground glass opacities, fibrotic reticulations and honeycombing) Whole lung fibrosis (% of only the fibrotic reticulations)	Minimal-to-mild	Mild-to-severe disease
Disease impact	All features should be met	Must have ≥1 feature
Feel	None	Yes
Function	None	Yes
Survive	N/A	Yes
Disease progression	Must have ≥1 feature for either category (attributable to ILD)	
Respiratory symptoms	New onset dyspnoea or cough	Advancing dyspnoea or cough
Spirometry with gas exchange	New decline	Advancing decline
Desaturation on exercise or exercise limitation	New desaturation and/or limitation	Advancing desaturation and/or limitation
Quantitative HRCT	New, larger extent of disease burden	Advancing extent of disease burden

CTD-ILD: CTD-interstitial lung disease; HRCT: high resolution CT; SSc-ILD: SSc associated interstitial lung disease.

of patients should not be determined by the behaviour of the treating physician. As an example, the recently completed phase III trial of tocilizumab shows a beneficial effect in a subset of patients who may have been characterized as subclinical ILD; in our original conception, this population would have fallen outside the scope of clinical ILD, not been treated and would not have benefitted from treatment [13]. Finally, progression should not be seen as a subset separate from subclinical or clinical ILD, but rather a property of either subset. In the original conception, progressive ILD was described as a state of advancing fibrotic disease on HRCT with escalation of respiratory symptoms and/or decline on serial lung physiology, gas exchange or both. In the revised version advancing symptoms, declining lung physiology and increased extent of ILD on HRCT mark the state of progression in either subclinical or clinical ILD. The critical revision here centres on recognizing that progressive SSc-ILD should be contextualized: a subclinical ILD patient with progression may not have the same disease mechanism or expected response to treatment as a clinical ILD patient with progression.

Expert classification

Forty-four of 83 (53%) of invited experts from 12 countries completed the survey, representing the following disciplines: rheumatology, $n = 26$; pulmonary medicine, $n = 16$; and thoracic radiology, $n = 2$ (Supplementary Table S2, available at *Rheumatology* online).

A majority of profiles achieved consensus along the three dimensions. The highest degrees of concordance were seen in severity (75%, or 60 of 80 baseline profiles) and risk of progression (71%, or 57 of 80 baseline profiles). Fewer profiles reached consensus for progression (60%, or 24 of 40 follow-up profiles) (Table 2). For each dimension, the majority subsets achieving consensus were as follows: severity–clinical ILD (92%, or 55 of 60), risk of progression–low risk of progression (54%, or 31 of 57), and progression–stable (71%, or 17 of 24 follow-up profiles).

Classification agreement between the two most common disciplines (e.g. pulmonology–rheumatology) did not differ in terms of the kappa statistic assessing inter-rater assessment for each of the three dimensions (Table 3). Agreement between pulmonologists and rheumatologists was not found to be different from the agreement within each discipline either. Kappa reported for severity was none whereas the risk of progression and progression were generally weak or moderate.

For those profiles achieving consensus and only assessing the relationship between two disciplines (e.g. radiology was excluded due to the low representation in participation), a χ^2 analysis assessed the proportion of each domain's outcomes (e.g. clinical ILD *vs* subclinical ILD) by the discipline (e.g. pulmonologist and rheumatologist), and did not show statistically disproportionate disagreement for each dimension (Table 3).

Table 4 reports the most frequently cited single item that experts used to influence their classification, as determined by the first item selected by the expert, representing their top choice in diagnostic importance. These data show that the items reported by experts were most influential in their classification for severity of ILD (in order of top ranked items) were forced vital capacity (FVC), HRCT quantitative total lung involvement (summed percentage of ground glass opacities, fibrotic reticulations and honeycombing), dyspnoea index (Baseline Dyspnoea Index/Transition Index), and diffusion capacity of carbon monoxide (DLCO). For progression, the top ranked items included FVC, HRCT total lung involvement, total lung fibrosis on HRCT, dyspnoea index, and DLCO. The highest ranked item used to assess risk of progression classification was a disease factor, specifically disease duration followed by FVC, HRCT total lung involvement and scleroderma-specific autoantibodies.

Discussion

To our knowledge, this is the first collaborative effort to establish a conceptual framework for SSc-ILD subsets. We created a literature-based, expert-informed rubric that characterizes SSc-ILD along three dimensions: disease severity, risk of progression and progression over time. This framework (i) was tested by having experts classify real-world patient profiles, (ii) reached agreement for all three dimensions, having a majority of patient profiles achieving consensus (≥75% concordance with other experts), and (iii) helped identify which items are most important in adjudicating between SSc-ILD subsets. Importantly, the framework does not include any specific values or cut-points in the definition of each subset. The goal of this work was to provide an inventory of clinical information necessary and general guidelines for implementation, to lead to a classification scheme along different dimensions. The result of this body of work is fundamental to the future development of classification criteria of SSc-ILD subsets and may provide a platform to expand to other fibrotic ILDs.

A majority of experts reached consensus on severity (75% of experts) and risk of progressive disease (71% of experts); this may reflect experts' familiarity with the basis of the framework, the extensive literature focusing on disease severity (e.g. epidemiologic data, expert opinion on determining which patients should receive treatment, inclusion criteria for SSc-ILD clinical trials) and risk of progression (e.g. identifying prognostic items that identify those with a concerning clinical

Table 2. Profiles assessed by dimension

	Severity		Risk of progression		Progression	
Number of profiles assessed	**80**		**80**		**40**	
Profiles achieving consensus, *n* (%)[a]	60 (75)		57 (71)		24 (60)	
Subset	Subclinical	3	High Risk	26	Improved	3
	Clinical	55	Low Risk	31	Progressive	4
					Stable	17
Cannot classify (based on the given information)		2		0		0
Profiles not achieving consensus, *n* (%)	20 (25)		23 (29)		16 (40)	

[a] A consensus was reached if ≥75% of experts in each group agreed.

Table 3. Agreement of classification by discipline, along dimensions of severity, risk of progression and progression

A. Determined by Kappa statistic

Kappa calculation	*n* (pair)[a]	Average *n* (profile)[b]	Mean	Bootstrapped mean (95% CI)[c]
Severity				
Between rheumatologists and pulmonologists	66	7.6	0.13	0.13 (0.00, 0.25)
Among rheumatologists	44	8.7	0.17	0.17 (−0.01, 0.45)
Among pulmonologists	17	6.6	0.20	0.18 (0, 0.25)
Risk of progression				
Between rheumatologists and pulmonologists	66	6.6	0.61	0.59 (0.49, 0.69)
Among rheumatologists	44	8.3	0.70	0.66 (0.51, 0.86)
Among pulmonologists	17	5.9	0.48	0.4618 (0.26, 0.66)
Progression				
Between rheumatologists and pulmonologists	66	3.1	0.56	0.51 (0.18, 0.70)
Among rheumatologists	44	3.5	0.78	0.70 (0.36, 0.95)
Among pulmonologists	17	3.1	0.29	0.24 (−0.00, 0.50)

B. Determined by χ^2 analysis

χ^2 calculation	Rheumatology	Pulmonology	*P*-value
Severity[d]			
Clinical ILD	205 (93.2%)	114 (89.8%)	0.26
Subclinical ILD	15 (6.8%)	13 (10.2%)	
Risk of progression			
High risk	97 (45.3%)	55 (46.2%)	0.88
Low risk	117 (54.7%)	64 (53.8%)	
Progression			
Progressive	17 (18.9%)	11 (20.0%)	0.20
Stable	57 (63.3%)	40 (72.7%)	
Improved	16 (17.8%)	4 (7.3%)	

[a] Number of paired used to calculate kappa statistics.
[b] Average number of profile in each pair.
[c] 100 bootstrap datasets, randomly selecting based on profile with replacement.
[d] 'Cannot tell' was removed from this calculation.

trajectory). The kappa statistic was poor for the severity classification (Table 3). The kappa statistic is known to be a chance-corrected statistic that is dependent on prevalence and in our case affected by the low prevalence of subclinical ILD classifications; for rare outcomes, very low kappa values do not necessarily reflect low rates of overall agreement [23]. Progressive SSc-ILD is perhaps a less well-defined concept in the literature, with few clinical trials providing clear operational definitions of progression in the form of inclusion/exclusion criteria. At the time the survey was conducted (January 2019–June 2019), the INBUILD trial, which focused on a population of patients with progressive fibrosing lung disease, had not yet been published (September 2019) [24]; this may provide insight as to why a smaller percentage of experts achieved consensus (60%). The exercise may also reflect the heterogeneous progressive nature of SSc-ILD, compared with severity or risk of progression.

Experts reported the FVC and extent of lung involvement on HRCT as the most important features used in classifying along severity and progression. The top priority on FVC and quantitative HRCT (whole lung involvement percentage) in this study likely reflects the impact of Goh *et al.*'s work and the subsequent data supporting the prognostic value in terms of disease severity and progression [25–29]. SSc-specific disease factors (e.g. factors describing SSc, without specific respiratory symptoms/lung function/imaging of the chest) were the most influential features in terms of determining risk of progression (accounting for 51% of all the items selected as the most important in classification), with disease duration as the most influential. This likely stems from the well-documented relationships to risk of progression, with shorter disease duration [30, 31] and presence of anti-SCL-70 (anti-topoisomerase I) increasing the risk for developing clinically significant SSc-ILD [32].

Classification agreement did not differ significantly between disciplines (e.g. pulmonology and rheumatology). The moderate degree of reliability between disciplines suggests that the invited authors all shared the same conceptual framework when completing the classification task for each dimension. One statistical consideration, given the relatively small number of evaluations per group, is the possibility that some profiles achieving or not achieving consensus could have been the result of chance alone and not a shared consensus.

Four limiting factors contextualize these results. First, the data in this initiative are generated from experts responsive to an invitation to participate; to avoid a selection bias, we invited a network broader than those with phone or email contact. Social media is playing a larger role in collaborative efforts in science [33, 34]. We broadcast this initiative using social media platforms and received interest from participants in several countries and from several disciplines. We selected only those respondents who have demonstrated considerable contribution to the field of ILD. Importantly, there were no expert participants from East Asian countries, although there was representation from South Asia. Pulmonologists who participated in this exercise (data shared by 13 of the 16) spend about half of their time dedicated to clinical practice (54%); of that clinical time, more than half (58%) is spent dedicated

Table 4. Importance based on percentage of items used in the classification of profiles along dimensions of severity, risk of progression, and progression

Domain with items used in classification	Severity		Risk of Progression		Progression	
	Rank between domains	Importance based on percentage selected	Rank between domains	Importance based on percentage selected	Rank between domains	Importance based on percentage selected
Demographics	5	Least influential	4	Less influential	—	Not ranked
Age, %		0		1		
Sex, %		0		1		
Race, %		0		1		
Disease factors	4	Less influential	1	Most influential	—	Not ranked
Systemic sclerosis subtype, %		3		7		
Disease duration, %		2		31		
ANA status, %		0		1		
Systemic sclerosis autoantibody status, %		2		11		
Modified Rodnan Skin Score, %		0		1		
Patient reported outcome measures	3	Influential	5	Least influential	3	Least influential
Baseline Dyspnoea Index/Transition Index, %		19		1		6
Leicester Cough Questionnaire, %		1		0		0
Patient global assessment, %		1		0		1
St George's Respiratory Questionnaire, %		3		1		2
Spirometry and gas exchange	1	Most influential	2	Very influential	1	Most influential
Forced vital capacity, %		29		17		48
Diffusion capacity of carbon monoxide, %		11		5		6
Quantitative high resolution chest CT	2	Very influential	3	Influential	2	Influential
Total lung involvement, %		25		15		29
Total lung fibrosis, %		5		6		8

to fibrotic ILDs and about 40% is spent on general pulmonary medicine/critical care medicine. Input from general pulmonologists should also be considered in the future to evaluate the conceptual framework's ease of use. Second, patients recruited from clinical trials tend to have more severe manifestations of lung disease than those not enrolled in trials. Knowledge that patient profiles were created from SLS-II patients may have biased experts to classify patients as 'clinical' rather than 'subclinical'. We sought to offset that bias with patients from our institution who did not participate in clinical trials, to provide experts with a cache of SSc patients with minimal to mild ILD. Third, a major limitation of the presented conceptual framework supposes that patient reported outcomes are measuring symptoms (e.g. dyspnoea, exercise limitation) attributed to SSc-ILD not confounded by other causes (e.g. pulmonary hypertension, anaemia, musculoskeletal disease, diaphragmatic weakness, smoking, deconditioning). Future work will require classification exercises to be based on more granular detail of the cardiorespiratory status of patients with SSc-ILD; this may allow for more generalizable interpretations of symptom assessment in the setting of real-world, co-occurring and potentially confounding features. Finally, the framework is the product of expert discussion that reflects an understanding of SSc-ILD in a particular time-dependent context and will require revisions as our understanding of the disease progresses. This project was launched in 2019 when phase III focuSSced data were being analysed. Notably absent from the framework are acute phase reactants, which may now be considered a marker of a progressive phenotype demonstrated in the focuSSced population. The framework in its current form will be updated with acute phase reactants in subsequent iterations. Future efforts working towards developing formal classification criteria of SSc-ILD will dovetail with the American College of Rheumatology's ongoing initiative to develop guidelines for screening and management of CTD-ILDs [35]. Additionally, there will need to be consideration for patient input in the classification to capture an element of lived experience with this disease not captured by patient reported outcome measures. There is an ongoing effort to get patients' input as part of the OMERACT CTD-ILD working group.

Johnson *et al.* 2018 [36] have identified a need for new SSc subset criteria, with the advent of an improved understanding of the disease (e.g. biomarkers, autoantibody profiles, genetic markers), and early disease identification, in the era of personalized medicine [36, 37]. The impetus for developing working definitions of SSc-ILD subsets is based on the same principles; this effort is timely in light of two treatments approved for the indication of SSc-ILD by the FDA [38, 39]. These data form the basis for a multi-dimensional assessment of SSc-ILD (severity, risk of progression and progression over time) and are a step towards building classification criteria for these subsets. Future work will include validation of the conceptual framework in a separate cohort of patients.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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