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Title

Evolution of high-resolution CT-scan in systemic sclerosis-associated interstitial lung disease: description and prognosis factors.

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Abstract

Objective: The aims of our study were to describe the evolution of interstitial lung disease (ILD) extent on HRCT scan in systemic sclerosis (SSc), to identify baseline prognostic factors associated with ILD evolution and to assess whether the evolution of pulmonary function tests (PFTs) correlated with this evolution.

Methods: 58 SSc with ILD (SSc-ILD) patients were included. All HRCT scans and PFTs available were collected. We modeled PFTs and HRCT scans evolution using linear mixed model with random effect.

Results: Patients underwent a median number of 3 HRCT scans (total n=203) and 5 PFTs (total n= 329), during a mean follow-up of 5.3 ± 4.9 years. Mean SSc duration was 2.5 ± 3.1 years at the diagnosis of ILD. Mean baseline ILD extent was $32.3 \pm 28.7\%$. We found a significant mean progression of ILD extent on serial HRCT scans of $0.92 \pm 0.36\%$ per year ($p=0.018$). Male sex, diffuse cutaneous SSc (dcSSc), presence of anti-topoisomerase 1 antibodies, a higher DLCO, limited ILD and a low coarseness score at baseline in bivariate analysis, and presence of antitopoisomerase 1 antibodies and a coarseness score of 0 in multivariate analysis, were associated with faster progression of ILD extent over time. There was a significant correlation between the progression of ILD extent and the decline of DLCO but only a trend for FVC. ILD extent at baseline and during follow-up was associated with survival.

Conclusion: Male sex, dcSSc, anti-topoisomerase 1 antibodies and a less severe ILD at baseline were associated with a faster progression of ILD over time. Evolution of DLCO significantly correlated with change in ILD extent on HRCT scan. Our study helps defining the profile of patients at risk of experiencing a progression of ILD on HRCT scans.

Keywords: Systemic sclerosis, interstitial lung disease, HRCT scans, pulmonary function test, DLCO.

I- Introduction

Interstitial lung disease (ILD) is a frequent complication of systemic sclerosis (SSc) and a leading cause of morbidity and mortality in this disease (1–4). Factors associated with the presence of ILD in SSc (SSc-ILD) are well known such as diffuse cutaneous SSc (dcSSc) and antitopoisomerase 1 antibodies (Ab) (5–8). Conversely, data on factors associated with ILD progression are limited. Identifying patients at risk of progression is important so treatment can be initiated early in the course of the disease (9–11), especially in a context of recent positive data with antifibrotic drug (12). Concerning the evolution of the pulmonary function tests (PFTs), Goh *et al.* found that an extensive SSc-ILD on high-resolution computed tomography (HRCT) scan at baseline was associated with a worse progression-free survival based on PFT worsening (13). In line with this result, the decline of FVC in the placebo group of the Scleroderma Lung Study (SLS) was greater during follow up in patients with a more severe ILD on baseline HRCT scan (9). In addition, we recently showed that pulmonary hypertension was associated with a faster decline of DLCO in patients with SSc-ILD (14). Wu *et al.* showed in patients with mild ILD on HRCT scans that a combined score using pulse oxygen saturation at the end of a six minutes walking test and a past or current history of arthritis was predictive of the evolution of PFTs at one year (15).

Concerning the evolution of SSc-ILD on HRCT scans during follow-up, data are even rarer. Hoffmann-Vold *et al.* recently showed that the annual fibrosis progression rate was $0.5 \pm 2.2\%$ and that baseline fibrosis and impaired FVC were predictors of an extension of fibrosis above 20% at the end of follow up (16). Yet, to our knowledge, no study has precisely described the fine evolution of SSc-ILD on serial HRCT scans and the factors associated with this evolution. To fill this gap, we designed this study to describe the evolution of SSc-ILD on serial HRCT scans using a linear mixed model with random coefficients and to identify baseline factors associated with ILD worsening on HRCT

scans. Finally, we investigated whether the evolution of the PFT parameters was correlated with the evolution of HRCT scans.

II- Patients and methods

1- Patients

Patients from our university hospital were retrospectively included from May 1991 until January 2014 if they fulfilled the following criteria: 1. diagnosis of SSc according to ACR/EULAR and/or to LeRoy's classification system (17–20), 2. presence of ILD on baseline HRCT scans, 3. available clinical evaluation at baseline and 4. at least one HRCT scan performed during follow up. As we choose to study the natural history of the disease, and not the disease course under immunosuppressive treatment, we stopped the follow-up of CT-scan and PFT when immunosuppressive treatment was introduced.

Exclusion criterion was the association with another connective tissue disease (overlap syndrome). In our university hospital, all patients with a new diagnosis of systemic scleroderma have a HRCT scan and PFT. Among 474 unselected patients in our SSc database (138 with SSc-ILD), we finally included 58 patients in our study (Flow Chart: see **Figure E1 in the online data supplement**). This study was approved by the Commission Nationale de l'Informatique et de la Liberté (No. DC-2008-642) and was in accordance with current French legislation. Patients gave their consent and data were accessed anonymously.

2- Clinical Data

Baseline was defined as the visit when the first HRCT scan diagnosing ILD was performed. Clinical data were collected in patients' medical files: gender, age at ILD diagnosis, subtype of SSc according to Leroy and Medsger (19), duration between onset of Raynaud's phenomenon and ILD, duration between first non-Raynaud's phenomenon

symptom and ILD, active or past history of smoking, dyspnea according to NYHA, presence of lung crackles, gastroesophageal reflux symptoms, and digital ulcer.

3- Biological Data

At baseline, we recorded hemoglobin (Hb) (g/dL), C reactive protein (CRP) (mg/L), antinuclear antibodies (ANA), anti-centromere antibodies, and anti-topoisomerase I (anti-SCL70) antibodies.

4- Echocardiography and Right Heart Catheterization

Left ventricular ejection fraction (LVEF) was recorded when available at baseline (n=41). Confirmed precapillary pulmonary hypertension (PH) was defined by a mean pulmonary artery pressure > 20 mmHg, pulmonary wedge pressure ≤15 mmHg and pulmonary vascular resistances ≥ 3 IU, at baseline or during follow-up, at right heart catheterization (RHC) (21) RHC was performed if echocardiography was suggestive of pulmonary hypertension.

5- Pulmonary Function Tests (PFTs)

All PFTs from baseline to the last visit, defined as the time of the last HRCT scan available, were collected, including FVC and TLC, DLCO corrected for hemoglobin, expressed in percentage of predicted value (22, 23).

6- High Resolution Computed Tomography (HRCT) scans

HRCT examinations were obtained according to standard ILD protocol including supine position always completed by prone images when abnormal infiltration was observed, obtained at deep inspiration. Slice thickness was 1 mm. Scans were volumetric. All the scans that were analyzed were judged to be of good quality. CT equipment was from the same manufacturer over time (Siemens Healthineers, Forchheim, Germany) with scanning

protocols for ILD always obtained with high resolution. Patients were longitudinally evaluated on the same CT scanner, excepts for those who had a CT follow-up after replacement of the CT unit. Image analysis is detailed in the **supplemental appendix in the online data supplement**. Briefly, all HRCT examinations were independently reviewed by two radiologists experienced in interstitial lung diseases (GK, MRJ), blindly from clinical data. HRCT scans were reviewed at six levels, adapted from (24).

At each level, the following features were quantified: (A) the overall extent of ILD, including both ground-glass opacification and reticular opacification, estimated to the nearest 5%; (B) the relative proportions (up to a total of 100%) of reticular pattern and ground-glass opacification in the overall interstitial lung disease; (C) the coarseness of fibrosis, (D) the extent of emphysema. Then, all HRCT scans were reviewed to define a semi-quantitative evaluation of ILD on the whole scan as follows: grade 1, predominant ground-glass opacification; grade 2, equal proportions of ground-glass opacification and reticular pattern; grade 3, predominant reticular pattern (25). Finally, the staging described by Goh *et al.* (13) was established for each patient: ILD was classified as limited or extensive, based on ILD initial extent on HRCT scan with in intermediary cases the use of FVC. HRCT scan were scored at five levels, and the extent of ILD was classified as limited (under 20% of pulmonary parenchyma), or extensive (above 20%). For indeterminate cases, ILD was considered as extensive if FVC was < 70% pred, and limited if FVC was \geq 70% pred.

Coarseness score and bronchiectasis score are defined in **supplemental appendix in the online data supplement**.

Discrepancies were reviewed jointly and resolved with consensus evaluation.

7- Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean and standard deviation in case of normal distribution and as median and interquartile range otherwise. The normality of the distribution was checked graphically and using the Shapiro-Wilk test. The primary outcome was the ILD extension and the primary exposure was the time. The evolution of ILD extent and HRCT scan parameters over time was analyzed using a linear mixed model to take into account the correlation between repeated measures within subjects by including a random coefficients (time and intercept); mean annual progression of ILD was estimated from regression coefficient of time. Normality of model residuals was checked with a normal probability plot. The association between each baseline factor and variation of ILD extent was studied using a linear mixed model with random coefficients (time and intercept) in bivariate and multivariable analyses). Significant baseline factors at the level of 0.05 in bivariate analyses were introduced in the multivariable model except for two factors: the proportion of GGO which was correlated with the coarseness score, and the baseline value of ILD extension (as ILD evolution is the dependent variable). A stepwise-backward selection at the level of 0.05 for each parameter of the model (baseline and interaction time*baseline) was performed. The association between the repeated measures of ILD extent on HRCT scan and PFTs parameters (DLCO and FVC) was assessed using the linear mixed model according to the method observed by Thiébaud *et al.* (26). Baseline values of DLCO, FVC and ILD extension were tested as prognostic factors of the survival in univariate analysis using Cox proportional hazard regression model. Longitudinal assessment of these variables were analyzed using time-dependent Cox model. We stopped the collection of follow up of CT scans and PFT at the time immunosuppressants were started to study the natural history of SSc-ILD.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

III- Results

1- Baseline characteristics

We included 58 patients with SSc-ILD. Baseline PFTs showed a mean DLCO of 70.1 ± 25.5 % of predicted value (pred), and a mean FVC of 96.4 ± 21.3 % pred. On HRCT, mean ILD extent at baseline was 32.3 ± 28.7 % (median 24.2 (8.3-53.3)). At the time of ILD diagnosis, mean disease duration since first non-Raynaud's phenomenon symptom was 2.5 ± 3.1 years, median 1 (0-4) year. ILD extent according to Goh *et al.* staging system was extensive in 40.3% of patients. Nine patients underwent a right heart catheterization, which showed a precapillary PH in all patients. Detailed baseline clinical, biological, functional and HRCT scan characteristics are shown in **table 1**.

2- Evolution on HRCT scans

All of the available HRCT scans (n=203) were evaluated, with a median number of 3 HRCT scans per patient (range 2-10), during a mean follow-up of 5.3 ± 4.9 years (309 patient-years). The median time period between the first HRCT and second HRCT was 12 months with an interquartile range from 6 to 22 months, and a range from 2 to 104 months. The mean annual progression of ILD extent was 0.92 ± 0.36 % (p=0.018) (**Figure 1A**).

3- Baseline parameters associated with the evolution of ILD extent on serial HRCT scans

In bivariate analysis, we found that male sex, dcSSc, presence of anti-topoisomerase 1 antibodies, absence of dyspnea (defined by NYHA I), Hb ≥ 13.4 g/dl and DLCO ≥ 60 % pred at baseline were associated with a faster progression of ILD extent. Among HRCT characteristics at baseline, limited ILD according to Goh *et al.* staging system, a coarseness score of 0, a proportion of ground glass opacities of 100% and a global score

of bronchiectasis of 0 were associated with a faster progression of ILD extent (**Table 2 and Figure 1 B, C, D**).

Conversely, neither age at diagnosis, disease duration, PH, GERD, digital ulcer, CRP, TLC, FVC, nor ILD grade at baseline were associated with the slope of progression of ILD extent.

In the multivariable analysis, only the presence of anti-topoisomerase 1 antibodies and a coarseness score of 0 remain associated with a faster progression of ILD extent. The limited ILD according to Goh et al. staging system and the DLCO \geq 60% pred at baseline were associated with baseline value of ILD extent and not with its evolution (**Table 3**).

4- Evolution of PFTs and correlation with the progression of ILD extent

a. Evolution of PFTs (figure 2)

Patients underwent a median number of 5 PFTs (range 1-16) for a total number of 329 PFTs. During follow up, DLCO declined significantly by -2.00% [95% CI: -2.85; -1.15] pred per year (p<0.001), FVC by -0.44% [95% CI: -0.87;-0.004] pred per year (p=0.048) and TLC by -0.85% [95% CI: -1.35;-0.35] pred per year (p=0.001).

b. Correlation between the evolution of ILD extent on HRCT scans and the evolution of PFTs

There was a significant correlation between the evolution of ILD extent on HRCT scans and the decline of DLCO during follow up.

For an increase of 1.32 point of percentage of ILD extent on HRCT scans in a year, DLCO decreased of 2.23 point of % pred in a year (p=0.014). There was a trend towards a correlation between the evolution of ILD extent on HRCT scans and the decline of FVC during follow-up, but it did not reach significance (for an increase of 1.07 point of percentage of ILD extent in a year, FVC decreased of 0.50 point of % pred in a year, p=0.085).

5- Predictors of survival

a- Baseline predictors of survival

At the end of follow up, 21 patients had died. In univariate analysis, we found that higher baseline values of ILD extent was associated with increased risk of mortality (HR 1.28 [95% CI: 1.08-1.52] p=0.005). There was only a trend between a higher DLCO at baseline and a decreased risk of mortality (HR 0.81 [95% CI: 0.66-1.00] p=0.050) . Baseline FVC value was not associated with survival (HR 0.89 [95% CI: 0.73-1.11] p=0.309).

b- Progression of ILD and survival

Then, we performed a longitudinal assessment using time dependent cox analysis and found that a higher DLCO was associated with a decreased mortality (DLCO HR 0.69 [95% CI: 0.52-0.92] p=0.010), while a higher ILD extent on HRCT scan was associated with a higher risk of death (HR 1.33 [95% CI: 1.10-1.61] p=0.003). Conversely, FVC was not associated with survival (0.97 [95% CI: 0.76-1.24] p=0.815)

IV- Discussion

The main results of our study were as follow: 1) The mean progression of SSc-ILD extent on HRCT scans was $0.92 \pm 0.36\%$ per year in our population; 2) We identified several clinical, biological and functional baseline factors associated with a faster progression of SSc-ILD extent over time: male gender, dcSSc, presence of anti-topoisomerase 1 antibodies, absence of dyspnea, $Hb \geq 13.4g/dl$ and $DLCO > 60\%$ pred at baseline 3) We identified several baseline HRCT scan characteristics associated with a faster progression of SSc-ILD extent over time: limited ILD according to Goh *et al.* staging system, a

coarseness score of 0, a proportion of ground glass opacities of 100% and a global score of bronchiectasis of 0; 4) In multivariate analysis, the presence of antitopoisomerase 1 antibodies and a coarseness score of 0 were associated with a faster progression of SSc-ILD extent 5) There was a correlation between the progression of ILD extent over time and the decline in DLCO but only a trend for FVC. 6) ILD extent at baseline and during follow-up was associated with survival.

First, the basal FVC seem high compared to the ILD extent on HRCT scans One explanation could be that we chosed to adapt the way to assess ILD extent on HRCT scans compared to the publication of Desai et al.(24) We decided to review the HRCT scans at 5 levels as in the Desay et al study, and to add a sixth level because SSc-ILD predominates in the lower lobes, which, in your opinion, was not sufficiently captured by the first 5 levels. This could have increased the mean ILD extent. Indeed, using only the first 5 levels, mean ILD extent was lower at 27.9% in our study. The mean annual progression of ILD extent was $0.92\% \pm 0.36$ per year. This is consistent with data from the placebo group of SLS with a progression of ILD extent of 2.2% at 12 months (27), and with the study of Hoffman-Vold *et al.*, which found an annual ILD progression rate of $0.5 \pm 2.2\%$ (16). Some baseline characteristics were associated with a faster progression of SSc-ILD extent on HRCT scan over time. Male gender has already been described as being associated with an ILD extent of more than 20% (16) and with end stage lung disease (28). Moreover, several studies found that male gender is associated with mortality in SSc-ILD (13, 29) and faster time to decline in DLCO (13). However, to our knowledge, the precise impact of male gender on HRCT scan evolution has not been described previously. Anti-topoisomerase 1 antibodies are known as a predictive factor for the presence of ILD in SSc (6), but to our knowledge it is the first time that they are described as associated with a faster progression of SSc-ILD extent on serial HRCT scan. Similarly, the diffuse type of SSc is known to be a risk factor for developing ILD (6) and was

described as a mortality factor in SSc-ILD (30), but it had not yet been described as a factor associated with a faster progression of ILD extent. Gilson *et al.* showed previously that the diffuse subtype of SSc was independently associated with a decrease in FVC over time (31), but their study included patients both with and without ILD at baseline, while all patients in our study had a SSc-ILD at baseline.

Other parameters associated with a faster progression of SSc-ILD extent on HRCT scan over time were more surprising, such as the absence of dyspnea and a DLCO>60%pred at baseline. The probable explanation is that the absence of dyspnea and a DLCO>60%pred reflect a more limited ILD, which was also associated in our study with a faster progression of ILD extent over time. It should be emphasized that, even if patients with a limited ILD at baseline are significantly progressing faster over time than patients with an extensive ILD at baseline, their final ILD extent at the end of the follow up is still lower than the final extent of patients with an extensive ILD at baseline. The explanations are not straightforward. One hypothesis is that the fibrosing process could be faster at the beginning and then reach a plateau with a more stable disease with a slower progression and a self-limitation. Our results could be interpreted as contradictory with other studies, which usually suggest that a more severe ILD at baseline (either on extent or on the severity of ILD) is associated with a worse outcome. In fact, there is no discrepancy as the different studies do not assess the same outcome parameters (**see table E1 in the online data supplement**). For example, Moore *et al.* found that an extensive ILD according to Goh *et al.* staging system on HRCT scan at baseline was associated with death, need for long term oxygen treatment or lung transplantation (32). Goh *et al.* have shown that an extensive ILD on baseline HRCT scan was associated with a more frequent decline of FVC and DLCO as defined by a drop of 10% and 15% from baseline, respectively (13). These studies did not assess whether an extensive ILD was associated or not with a faster progression of ILD extent on serial HRCT scan as in our study. Indeed, only a few studies

focused on ILD-SSc evolution on HRCT scan. Hoffmann-Vold *et al.* recently found in 197 patients with SSc-ILD that a lower FVC and DLCO at baseline were associated with ILD extent of more than 20% on HRCT scan at the end of follow-up. However, a final ILD extent of more than 20% is not synonymous with a faster progression of ILD extent over time as patient with ILD extent of more than 20% can be stable without any progression at all (16). Wangkaew *et al.* studied the evolution of ILD on HRCT scan but did not evaluate the correlation with baseline HRCT scan parameters (33).

In our study, FVC slightly decreased by $0.43 \pm 0.24\%$ pred per year while DLCO had a significant and higher decline of $2.00 \pm 0.36\%$ pred per year. The small decline in FVC is in line with other studies, some of them even finding a stability of FVC over time (14, 29). We found a significant correlation between the progression of ILD extent on HRCT scan and the decline of DLCO (% predicted) during follow up, and a trend for FVC, as previously reported (31, 33).

We found that a higher ILD extent on HRCT scan at baseline and during follow up, and a lower DLCO during follow up with only a trend for baseline DLCO, was associated with an increased risk of death while baseline and follow up FVC were not a prognostic factor in our study. In SLS I and II patients, Volkmann *et al.* identified the decline in FVC and in DLCO over 2 years as an independent predictor of mortality (34). In the study of Goh *et al.* composed by 70% of limited SSc-ILD, the FVC decline at 1 year was associated with mortality only in the extensive group. At 2 years, change in FVC was not associated with survival, while a decline in DLCO was significant (35). The absence of association between baseline/follow up FVC with mortality in our study could be explained by the majority of patients having limited ILD extension and the lack of power. Baseline ILD extent is already known as a prognostic factor (13, 32). The original part of our study is to show that beyond the baseline ILD extent, ILD extent on HRCT scan during follow up is also a prognosis factor.

Our study has some limitations mostly due to the retrospective design. Our sample size is limited. The multivariate analysis could only be performed on 47 patients. So, such a study requires a larger development sample to confirm the results. The interval between HRCT examinations was variable, but this was taken into account by our statistical model. We used a visual assessment of HRCTs to quantify the extent of ILD, which may be less objective than a fully quantitative approach: 50 of the 58 patients included in this CT follow-up evaluation had the baseline examination acquired prior to the installation of the PACS system in our hospital centre. As a consequence, corresponding images were not stored on a digital support but printed on films, thus precluding any quantitative approach. We stopped the collection of follow-up of CT scan and PFT at the time immunosuppressants were used, because it could have influenced the natural history and our study was not designed and sufficiently powered to address the role of these drugs in SSc-ILD. Our study has also some strengths including a fine phenotyping of patients and few missing data.

In conclusion, in this study analyzing the evolution of SSc-ILD on serial HRCT scans, we found an annual progression of ILD extent of $0.92 \pm 0.36\%$. Patients with a less severe and less extensive ILD at baseline were more likely to experience a faster progression of ILD extent on serial HRCT scans during follow-up. There was a correlation between the progression of ILD extent and the decline of DLCO over time. We found that a higher ILD extent on HRCT scan at baseline and during follow-up, and a lower DLCO during follow-up, was associated with an increased mortality. Our study helps define the profile of patients who are going to experience a progression of ILD on HRCT examinations. Further studies are mandatory to confirm these results.

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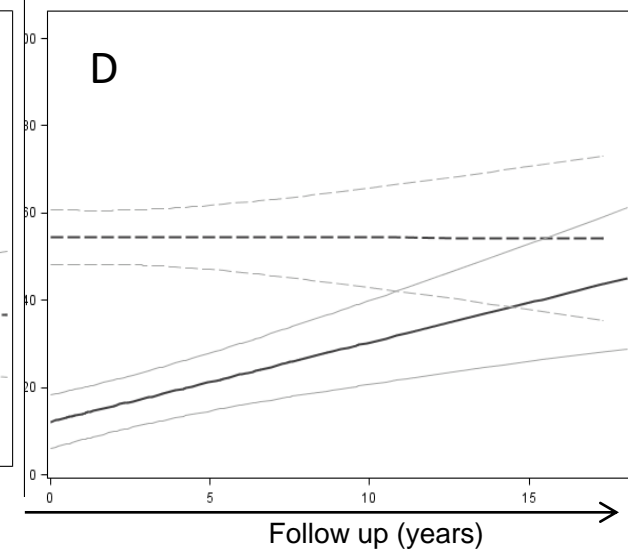
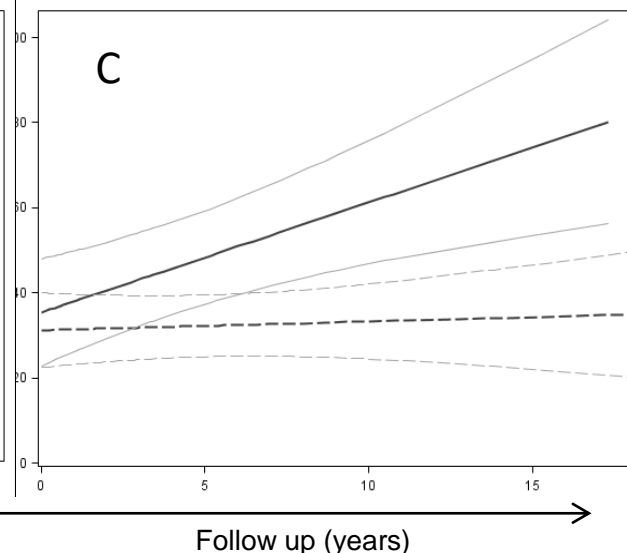
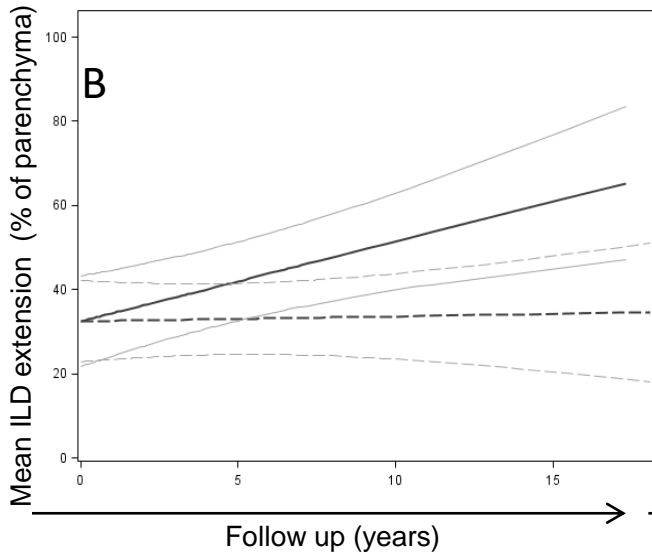
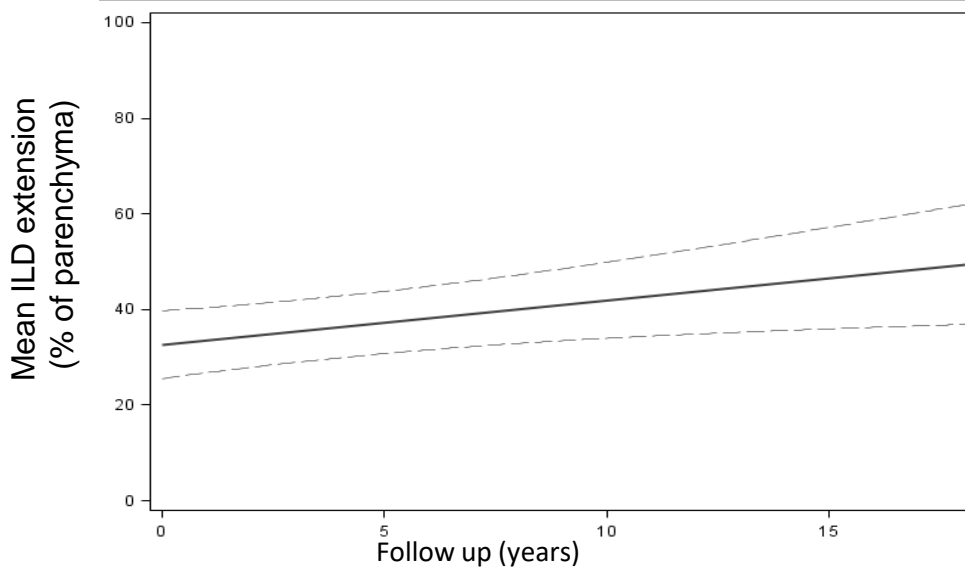
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FIGURE LEGENDS

Figure 1. A Mean progression of ILD extension. The solid line corresponds to the mean ILD extension, the dashed lines to the 95% confidence interval. **B C D** Mean evolution of ILD extension according to some illustrative baseline parameters, using the linear mixed model with random coefficients. The solid line corresponds to the mean, the dashed lines to the 95% confidence interval. **B:** Patients with a diffuse cutaneous SSc had a faster progression of ILD extension than patients with limited cutaneous SSc in bivariate analysis ($1.89 \pm 0.61\%$ vs $0.11 \pm 0.52\%$ per year, $p=0.030$). **C:** Male sex patients had a faster progression of ILD extension than female patients in bivariate analysis ($2.58 \pm 0.80\%$ vs $0.20 \pm 0.50\%$ per year, $p=0.014$). **D:** Patients with a limited ILD extension according to Goh *et al.* staging system had a faster progression of ILD extension than patient with an extensive ILD according to Goh *et al.* ($1.73 \pm 0.46\%$ vs $-0.22 \pm 0.70\%$ per year, $p=0.022$).

Figure 2. Individual trajectories of the 58 patients (in black) and mean evolution (in bold) of diffusing capacity of the lung for carbon monoxide (DLCO), forced vital capacity (FVC) and total lung capacity (TLC) using the linear mixed model with random coefficient. Mean [95%CI] DLCO decline was -2.00% $[-2.85;-1.15]$ per year ($p<0.001$). Mean [95%CI] FVC decline was -0.44% $[-0.87;-0.004]$ per year ($p=0.048$). Mean [95%CI] TLC decline was -0.85% $[-1.35;-0.35]$ per year ($p=0.001$).

A



— Diffuse cutaneous SSC
- - - Limited cutaneous SSC

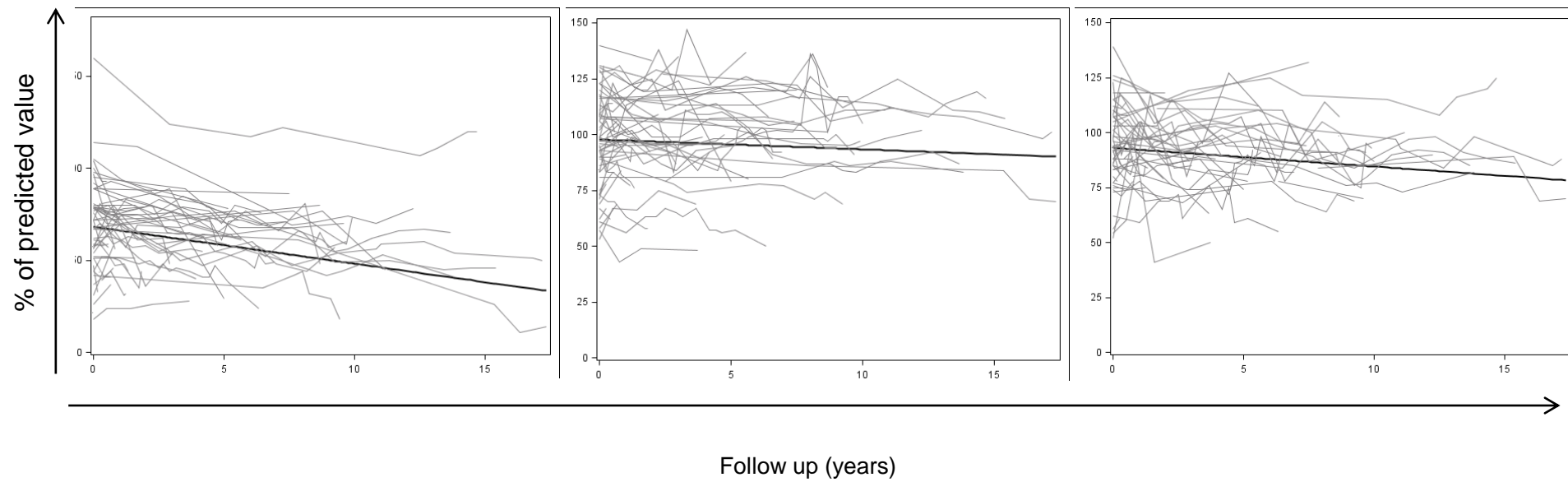
— Male
- - - Female

— Limited ILD extension according to Goh *et al.*
- - - Extensive ILD extension according to Goh *et al.*

DLCO

FCV

TLC



1 **Table 1.** Baseline characteristics.

	All patients N=58	Limited cutaneous SSc N=32 (55.2%)	Diffuse cutaneous SSc N=26 (44.8%)	p
Female, n (%)	39 (67.2)	28 (87.5)	11 (42.3)	< 0.001
Age at ILD diagnosis, years	54.5 ± 14.9	59.1 ± 13.2	48.7 ± 15.2	0.007
Disease duration since RP, years	4 (1-10)	4 (1-10)	4 (1-6)	0.37
Disease duration since first non RP symptom, years	1 (0-4)	1 (0-3)	2 (0-5)	0.57
Ever smoker, n (%)	13 (23.2)	7(23.3)	6 (23.1)	0.98
Dyspnea (NYHA), n (%)				0.34
I	31 (53.5)	15 (46.9)	16 (61.5)	
II	18 (31.0)	10 (31.2)	8 (30.8)	
III	9 (15.5)	7 (21.9)	2 (7.7)	
IV	0 (0.0)	0 (0.0)	0 (0.0)	
LVEF < 60%, n (%)	5 (12.2)	2 (8.7)	3 (16.7)	NA
Precapillary PH, n (%)	9 (15.5)	7 (21.9)	2 (7.7)	0.17
Crackles, n (%)	23 (40.3)	14 (45.2)	9 (34.6)	0.42
GERD, n (%)	32 (55.2)	17 (53.1)	15 (57.7)	0.73
Digital ulcer (active or past history), n (%)	19 (32.8)	7 (21.9)	12 (46.1)	0.050
Hb, g/dL	13.3 ± 1.5	13.1 ±1.4	13.6 ± 1.7	0.25
CRP, mg/L	3.0 (3.0-4.0)	3.0 (3.0-3.1)	3.1 (3.0-5.0)	0.074
ANA, n (%)	56 (96.5)	31 (96.8)	25 (96.1)	NA
ACA, n (%)	10 (17.9)	9 (29.0)	1 (4.0)	0.031
SCL70, n (%)	38 (67.9)	18 (58.1)	20 (80.0)	0.081
Anti-RNA polymerase III	0	0	0	
PFT, % of predicted value				
DLCO, %	70.1 ± 25.5	71.0 ± 21.4	69.1 ± 29.3	0.79
FVC, %	96.4 ± 21.3	98.9 ± 21.6	93.8 ± 21.0	0.38
TLC, %	93.9 ± 18.6	96.7 ± 19.1	90.1 ± 17.7	0.22
RV, %	98.0 ± 32.0	100.8 ±31.4	94.9 ± 33.2	0.53
FRC, %	99.0 ±30.0	101.4 ± 30.3	96.1 ± 30.2	0.56
HRCT				
ILD extension (% of parenchyma)	24.2 (8.3-53.3)	20.5 (6.3-53.3)	25.9 (10.0-58.3)	0.52
Proportion of GGO (% of ILD)	100.0 (86.0-100.0)	98.8 (80.9-100.0)	100.0 (90.0-100.0)	0.48
Extension of reticular pattern (% of parenchyma)	0.0 (0.0-4.8)	0.1 (0.0-6.0)	0.0 (0.0-2.4)	0.54
Coarseness score	0.0 (0.0-6.0)	6.0 (0.0-6.0)	0.0 (0.0-6.0)	0.64
Global score of bronchiectasis	0.0 (0.0-6.0)	6.0 (0.0-8.2)	0.0 (0.0-6.0)	0.054
Extensive ILD (Goh et al. staging system), n (%)	23 (40.3)	13 (41.9)	10 (38.5)	0.79
ILD grade, n (%)				NA
1	44 (76.4)	23 (71.9)	21 (80.8)	
2	10 (16.7)	7 (21.9)	3 (11.5)	
3	4 (6.9)	2 (6.2)	2 (7.7)	
Emphysema extension (% of parenchyma)	0.1 ± 0.5	0.4 ± 0.9	0.1 ± 0.1	NA

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3 Table 1. Baseline characteristics.

4 Values are expressed as mean±standard deviation or median (first quartile-third quartile),
5 unless otherwise indicated.

6 SSc: systemic sclerosis, ANA: antinuclear antibodies, ACA: anti-centromere antibodies,
7 SCL70: anti-topoisomerase I antibodies, RNAIII: anti-RNA polymerase III antibodies, ILD:
8 interstitial lung disease, RP: Raynaud's phenomenon, LVEF: left ventricular ejection
9 fraction, PH: pulmonary hypertension, SRC: scleroderma renal crisis, GERD:
10 gastroesophageal reflux disease, Hb: hemoglobin, CRP: C reactive protein, PFT:
11 pulmonary function test, DLCO: diffusing capacity of the lung for carbon monoxide,
12 DLCO/VA: transfer coefficient for the diffusion of CO, FVC: forced vital capacity, TLC: total
13 lung capacity, RV: residual volume, FRC: functional residual capacity, HRCT: high
14 resolution computed tomography, ILD: interstitial lung disease, GGO: ground glass
15 opacification, NA: not applicable.

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3 **Table 2.** Bivariate analysis of clinical and biological parameters at baseline

4 associated with the evolution of ILD extension on serial HRCT.

	Mean progression of ILD extension (%/year)	SE	P
Gender			0.014
<i>men</i>	2.58	0.80	
<i>women</i>	0.20	0.50	
SSc subtype			0.030
<i>limited</i>	0.11	0.52	
<i>diffuse</i>	1.89	0.61	
Smoker			0.57
<i>No</i>	0.79	0.46	
<i>Yes</i>	1.46	1.06	
Age at ILD diagnosis			0.94
< 54	0.96	0.54	
≥ 54	0.90	0.55	
Duration since RP, years			0.41
< 4	1.28	0.66	
≥ 4	0.61	0.48	
Duration since FNRP symptom, years			0.70
= 0	0.65	0.71	
≥ 1	1.00	0.56	
Dyspnea			0.044
<i>No</i>	1.87	0.59	
<i>Yes</i>	0.27	0.52	
PH			0.23
<i>No</i>	1.15	0.434	
<i>Yes</i>	-0.11	0.94	
Crackles			0.083
<i>No</i>	1.80	0.56	
<i>Yes</i>	0.41	0.55	
GERD			0.58
<i>No</i>	0.67	0.61	
<i>Yes</i>	1.11	0.52	
Digital ulcer (actual or past history)			0.53
<i>No</i>	1.08	0.45	
<i>Yes</i>	0.54	0.72	
Hb, g/dl			0.029
< 13.4	-0.03	0.70	
≥ 13.4	2.12	0.66	
CRP, mg/dl			0.45
≤ 3	1.48	0.65	
> 3	0.75	0.72	
Anti-topoisomerase 1 antibodies			0.034
<i>No</i>	-0.74	0.80	
<i>Yes</i>	1.29	0.50	
HRCT parameters			
ILD extension according to Goh <i>et al</i> staging system			0.022
<i>Limited</i>	1.73	0.46	
<i>Extensive</i>	-0.22	0.70	
ILD extension			0.023

< 20%	1.83	0.52	
> 20%	0.11	0.53	
ILD grade			0.42
1	1.21	0.45	
2	-0.66	1.41	
3	0.49	1.35	
Coarseness score			0.008
0	2.07	0.51	
> 0	0.25	0.44	
Global score of bronchiectasis			0.008
0	1.91	0.50	
> 0	-0.13	0.57	
Proportion of GGO			0.030
< 100 %	0.32	0.46	
100 %	1.84	0.51	
PFT parameters, % of predicted value			
DLCO			0.011
< 60%	-0.69	0.84	
≥ 60%	1.74	0.41	
FVC			0.92
≤ 97%	1.21	0.67	
> 97%	1.12	0.55	
TLC			0.28
≤ 94 %	0.56	0.68	
> 94 %	1.50	0.55	

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2 ILD: interstitial lung disease, SSc: systemic sclerosis, RP: Raynaud’s phenomenon,

3 FNRP: first non-Raynaud’s phenomenon symptom, PH: pulmonary hypertension,

4 GERD: gastroesophageal reflux disease, Hb: hemoglobin, CRP: C reactive protein,

5 HRCT: high resolution computed tomography, GGO: ground glass opacification, PFT:

6 pulmonary function test, DLCO: diffusing capacity of the lung for carbon monoxide,

7 DLCO/VA: transfer coefficient for the diffusion of CO, FVC: forced vital capacity, TLC:

8 total lung capacity, RV: residual volume, FRC: functional residual capacity , GGO:

9 ground glass opacification, SE: standard error.

10 We used the median as the cut off for TLC, FCV, because it was not statistically

11 possible to use the lower limit of normal, given the small sample size. We also used

12 the median (54) as the cut of for the age at ILD diagnosis.

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1 **Table 3.** Multivariable analysis of clinical and biological parameters at baseline
 2 associated with the evolution of ILD extension on serial HRCT.

	Mean baseline value of ILD extent (%)	Standard Error	p-value	Mean progression of ILD extent (%/year)	Standard Error	p-value
Intercept	29.17	7.21	-	-	-	-
Time	-	-	-	-1.65	0.98	0.099
Anti-topoisomerase 1 antibodies	0.13	6.01	0.98	2.57	0.93	0.010
ILD extension according to Goh <i>et al</i> staging system (Extensive)	35.23	6.31	<0.001	-	-	-
Coarseness score = 0	-3.41	5.62	0.55	2.52	0.86	0.005
DLCO >60%	-13.76	6.25	0.031	-	-	-

3 ILD: interstitial lung disease, DLCO: diffusing capacity of the lung for carbon monoxide.

4 The multivariable model was performed on 47 patients.

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