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Facteurs prédictifs d'évolution scanographique de la Pneumopathie Interstitielle Diffuse liée à la Sclérodermie Systémique

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Liste des Abréviations

SSc : sclérodermie systémique / systemic sclerosis

PID / ILD : pneumopathie interstitielle diffuse / interstitial lung disease

PID-SSc / SSc-ILD : PID liée à la SSc / SSc related ILD

HTAP / PAH : hypertension artérielle pulmonaire / pulmonary arterial hypertension

GGO : ground-glass opacification

EFR / PFT : épreuve fonctionnelle respiratoire / pulmonary function test

CVF / FVC : capacité vitale forcée / forced vital capacity

CPT / TLC : capacité pulmonaire totale / total lung capacity

DLCO : diffusion libre du monoxide de carbone / diffusing capacity of the lung for carbon monoxide

RGO / GERD : reflux gastro œsophagien / gastroesophageal reflux disease

TDM / HRCT : tomodensitométrie / high resolution computed tomography

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Abstract

Introduction: Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in systemic sclerosis (SSc). While factors associated with the presence of ILD in SSc (SSc-ILD) are identified, those associated with worsening of ILD are scarcer as are studies assessing the evolution of ILD on HRCT. However, it is important to identify patients at risk of ILD worsening because treating worsening ILD by immunosuppressants appears as a valuable strategy. Thus, the aims of our study are: to describe the evolution of HRCT extension and patterns of SSc-ILD, to identify baseline prognostic factors of ILD worsening on HRCT and to investigate whether the evolution of pulmonary function tests (PFTs) parameters are correlated with the evolution on HRCT.

Patients and methods: We included 58 SSc patients with HRCT proven ILD, with at least two HRCT available, and collected clinical and biological data as well as PFT at baseline. We collected all HRCT and PFTs available during follow-up. ILD characteristics were evaluated on six levels for each HRCT. We modelized PFTs and HRCT evolution using linear mixed model with random coefficients.

Results: Mean ILD extension at baseline was 32.3 ± 28.7%. During a mean follow-up of 5.3 ± 4.9 years, we found a mean progression of ILD extension of 0.92 ± 0.36% per year (p=0.018). Male sex, anti-topoisomerase 1 antibodies, diffuse cutaneous SSc were associated with faster progression of ILD extension. Limited ILD according to Goh *et al*. staging system, lower ILD extension at baseline, coarseness score at zero, ILD composed of 100% of ground glass opacification (GGO) and negative bronchiectasis score on baseline HRCT were associated with a faster progression of ILD extension. We also found a decline of DLCO, FVC and TLC during follow-up. There

was a significant correlation between the progression of ILD extension on HRCT and the decline of DLCO, but not with the evolution of FVC.

Conclusion: Our patients had a high ILD extension at baseline, but had slight functional impairment. Patients with less severe and less extensive disease at baseline were more likely to experiment a progression of ILD extension during follow up. To our knowledge, this is the first study that highlighted the diffuse form of the disease as a worsening factor of SSc-ILD. FVC might not be the best mirror of ILD progression. Our study helps to define the profile of patients who are going to experience a progression of ILD on HRCT.

I- Introduction Générale

La sclérodermie systémique (SSc) est une connectivite caractérisée par une fibrose systémique et cutanée associée à une microangiopathie et une activation du système immunitaire. Elle atteint principalement les femmes (sexe ratio ⅙) et débute en moyenne entre 45 et 65 ans (1). La SSc est une maladie rare dont l'épidémiologie varie selon les études et les pays. Aux USA, l'incidence est estimée à 5.6 cas pour 100000 personnes par an et la prévalence entre 13.5 et 18.4 pour 100000 personnes (2). En France, la prévalence est estimée à 15.8 pour 100000 habitants (3).

Le diagnostic repose sur un faisceau d'éléments cliniques et paracliniques, en particulier immunologiques. Des critères de classification de la maladie ont été proposés en 2013 (critères reposant sur les recommandations ACR/EULAR), comportant les paramètres suivants : l'infiltration cutanée, l'existence d'un phénomène de Raynaud, la présence de lésions pulpaires, de télangiectasies, de microangiopathie des capillaires unguéaux, d'hypertension artérielle pulmonaire (HTAP) ou de pneumopathie interstitielle diffuse (PID), et la présence d'autoanticorps spécifiques de la SSc que constituent les anticorps anti-centromères, les anticorps anti-RNA polymérase III et les anticorps anti-topoisomérase 1 (anti-SCL70) (4).

Classiquement, on individualise deux groupes de patients sclérodermiques selon l'extension de l'atteinte cutanée : les patients présentant une forme cutanée limitée, pour lesquels l'atteinte cutanée ne s'étend pas en amont des coudes et des genoux, et les patients présentant une forme cutanée diffuse, pour lesquels l'atteinte cutanée remonte au-dessus des coudes et/ou des genoux, ou touche le tronc (5,6).

Au-delà de l'atteinte cutanée, la SSc peut se manifester par diverses atteintes cliniques : articulaire, musculaire, du tractus digestif, HTAP, cardiopathie, PID, crise rénale sclérodermique (7). Il existe d'un patient à l'autre une grande variabilité de présentation clinique tant par le type d'organe touché que par la sévérité de l'atteinte présentée, qui conditionnent le pronostic des patients. Comparé aux sujets sains, le *hazard* ratio de mortalité des patients atteints de sclérodermie est estimé à 3.5 (8).

Parmi les atteintes systémiques, l'atteinte pulmonaire est une des premières causes d'hospitalisation et de mortalité. La proportion de patients dont le décès est lié à la PID est estimée autour de 30 à 35% (9,10)**.** La survie à dix ans des patients présentant une atteinte pulmonaire est estimée à 59% (11).

La prévalence de la PID associée à la SSc (PID-SSc) est très variable selon les études, de 16 à plus de 90%, en fonction des critères diagnostics et des examens de dépistage utilisés (12–16). Actuellement, l'examen diagnostic de référence est la tomodensitométrie (TDM) haute résolution, permettant la mise en évidence de PID chez des patients asymptomatiques (12,17). Les biopsies pulmonaires sont rarement réalisées mais ont permis d'identifier une histologie de pneumonie interstitielle non spécifique (NSIP) chez 77,5% des patients, bien plus fréquemment qu'une pneumonie interstitielle usuelle (UIP) (7.5%) ou qu'une fibrose évoluée ne permettant pas de classification (7.5%) (18,19).

La NSIP correspond en TDM à des opacités en verre dépoli majoritaires, prédominant dans les bases, périphériques, symétriques, pouvant être isolées ou associées à des opacités réticulaires et des bronchectasies de traction, avec peu de rayon de miel, alors que l'UIP est caractérisée par des réticulations prédominantes, du rayon de miel et peu de verre dépoli (20,21).

Pour analyser le retentissement fonctionnel de la PID, les épreuves fonctionnelles respiratoires (EFR) constituent l'examen de référence. Les paramètres les plus importants dans l'évaluation de la PID sont la capacité vitale forcée (CVF), la capacité pulmonaire totale (CPT) et la diffusion libre du monoxyde de carbone (DLCO), à la recherche d'un syndrome restrictif (défini par une CPT inférieure à 80% de la théorique) et d'une baisse de DLCO qui peut précéder la perte de volume, témoignant de l'altération des échanges gazeux (22,23). Les EFR sont également utiles dans le suivi, compte-tenu de leur caractère non invasif et non irradiant, permettant d'évaluer l'évolution du retentissement fonctionnel respiratoire de la PID de façon répétée.

Les profils de sévérité et d'évolution de la PID-SSc sont très variables, nécessitant une surveillance régulière. Ainsi, dans une étude de Steen *et al.* en 1994, parmi des patients sclérodermiques non sélectionnés, 27% présentaient une CVF entre 75 et 50% de la théorique, et 13% une CVF inférieure à 50% au cours du suivi (24). Les premières années de la maladie sont les plus à risque de voir apparaitre une atteinte sévère (15). De plus, le déclin fonctionnel semble plus important chez les patients présentant une PID sévère dès le diagnostic, dans les premières années d'évolution de la PID (24,25).

Un traitement immunosuppresseur est proposé lorsque la PID s'aggrave, ce qui nécessite une évaluation clinique et fonctionnelle régulière afin de détecter au plus tôt une aggravation respiratoire (26). La mise en évidence de facteurs de risque d'aggravation de la PID permettrait de distinguer les patients nécessitant une surveillance rapprochée, afin d'envisager un traitement immunosuppresseur précocement, ce traitement ne permettant souvent que de stabiliser la PID (27).

Alors que les facteurs de risque de développer une PID sont relativement bien identifiés (SSc de forme cutanée diffuse, présence d'anticorps anti-SCL70, âge plus élevé au diagnostic, CVF ou DLCO initiale plus basse, effet protecteur des anticorps anti-RNA-polymerase III) (14,24,28–31), les facteurs associés à l'aggravation d'une PID existante ont fait l'objet de peu d'études, aux schémas et aux profils de patients différents, avec des résultats discordants. Ainsi, en 1994, Steen *et al.* ont étudié un sous-groupe de patients présentant une aggravation fonctionnelle d'une atteinte restrictive modérée à sévère, mais aucun facteur pronostic n'a pu être identifié (24). Dans l'étude de Goh *et al*. en 2008, le caractère extensif de l'atteinte pulmonaire initiale (défini par une atteinte supérieure à 20% du parenchyme pulmonaire en TDM, ou en cas d'atteinte égale à 20% par une CVF inférieure à 70% de la théorique) était prédictif d'une moins bonne survie et d'un déclin de CVF et de DLCO (11). Dans l'étude de Gilson *et al*. en 2010, chez des patients non sélectionnés avec ou sans atteinte pulmonaire interstitielle initiale, seule la forme diffuse était prédictive d'un déclin fonctionnel défini par une diminution d'au moins 10% de CVF ou 15% de DLCO (32). Dans le groupe placebo d'un essai clinique évaluant l'efficacité du cyclophosphamide dans la PID-SSc (Scleroderma Lung Study), le sous-groupe des patients avec PID sévère sur la TDM initiale présentait un déclin annuel de la CVF plus important lorsque la maladie évoluait depuis moins de deux ans. Le déclin annuel de CVF n'était pas influencé par la présence d'anticorps anti-SCL70 (25). En 2015, l'équipe de Hoffmann-Vold a identifié, parmi des patients avec ou sans PID initiale, que le taux annuel de progression de la PID était corrélé au déclin de CVF, mais pas avec l'évolution de la DLCO. Dans cette étude, un sous-groupe de patients avec une PID touchant initialement moins de 20% du parenchyme pulmonaire voyait l'extension de la PID dépasser 20% au cours du suivi. Cette sous-population était caractérisée par une

durée d'évolution de la SSc plus courte que les autres groupes de patients (33). Dans un sous-groupe de patients présentant une aggravation scanographique des lésions de PID, Launay *et al.* ont identifié un score de dyspnée initial plus sévère et une moindre fréquence des crépitants à l'auscultation comme facteurs prédictifs d'une progression scanographique (14).

Ainsi, les études divergent sur les facteurs pronostiques d'évolution de la PID-SSc, et la littérature manque d'études évaluant l'évolution scanographique de la PID et ses facteurs prédictifs. Or, il est essentiel d'identifier les patients à risque d'aggravation qui pourraient relever d'un traitement immunosuppresseur précoce.

Ainsi, les objectifs de notre étude sont :

- de décrire l'évolution scanographique de la PID-SSc
- d'identifier des facteurs pronostics initiaux d'évolution scanographique de la PID-SSc
- de déterminer si l'évolution des paramètres EFR est corrélée à l'évolution tomodensitométrique.

II- Introduction

Systemic sclerosis (SSc) related interstitial lung disease (ILD) is a leading cause of morbidity and mortality in SSc.(9,10). Ten-year survival is estimated at 59% (11). ILD occurs in 16 to 90% of SSc patients (12–16), depending on the population studied and the diagnostic criteria used. SSc related ILD (SSc-ILD) develops in the first years of the disease (15,25), with various severity profiles (24). It is crucial to identify patients with pulmonary involvement at high risk of worsening in order to treat them early (26,27). High resolution computed tomography (HRCT) is one of the key tests to assess ILD (12,17). It usually shows bilateral and symmetrical ground-glass opacification (GGO) with basal and subpleural predominance, reticular pattern opacity which may be associated with traction bronchiectasis, and less frequently honeycombing (20,21). Lung function assessment includes at least spirometry with forced vital capacity (FVC), plethysmography with total lung capacity (TLC) and single breath diffusing capacity of the lung for carbon monoxide (DLCO) (22,23).

Whereas prognostic factors of ILD onset are identified (diffuse cutaneous disease, low baseline FVC or DLCO, anti-topoisomerase 1 antibodies, and a protective effect of anti-RNA polymerase III antibodies) (14,24,28–31), data about those associated with ILD worsening are scarce. Steen *et al.*, in 1994 identified a subgroup of patients with functional worsening from moderate to severe ILD, but failed to identify any prognostic factor (24). Goh *et al.*, in 2008, determined a staging system for extensive disease and found that an HRCT extension threshold of more than 20% (and in indeterminate cases a FVC threshold below 70% of predicted value) was associated with increased mortality and lower progression free survival (11). In Gilson *et al*. in 2010, on unselected patient with or without ILD at baseline, only diffuse SSc was associated

with a decrease of more than 10% of FVC or more than 15% of DLCO (32). In the placebo group of the scleroderma lung study (SLS, a trial evaluating the efficacy of cyclophosphamide in SSc-ILD), the decline of FVC was greater in the group with severe ILD on baseline HRCT, more pronounced if the disease had lasted for less than two years. The profile of antibodies was not predictive of the decline of FVC (25). Hoffmann-Vold *et al*. in 2015 found that progression of ILD extension in HRCT was associated with the decline of FVC but not with the evolution of DLCO. In this study, the subgroup of patients with a disease duration of less than three years had a significantly higher ILD progression (33). Launay *et al.* found that a more severe dyspnea score and less frequent crackles at baseline were predictive of progression of ILD extension in a subgroup of patients with SSc-ILD involving less than 50% of parenchyma at baseline. Neither gender, auto antibody profile nor baseline PFT were associated with the progression of ILD in this study (14).

Thus, those studies diverge on the prognostic factors of SSc-ILD progression, and the literature lacks studies evaluating the evolution of SSc-ILD on HRCT and its predictive factors. However, it is essential to identify patients at risk for worsening to consider early immunosuppressive therapy, which often only allows stabilization of ILD (27).

Thus, the aims of our study are:

- to describe the evolution of HRCT aspects of SSc-ILD
- to identify baseline prognostic factors of ILD worsening on HRCT
- to investigate whether the evolution of the PFT parameters are correlated with the HRCT evolution.

III- Patients and methods

1- Patients

To be included, patients followed in the department of internal medicine in Lille, France, from May 1991 until January 2014 had to fulfill the following criteria:

1) diagnosis of SSc according to ACR/EULAR and/or to LeRoy's classification system (4–6)
2) presence of ILD on HRCT
3) two or more HRCT available

Exclusion criteria were the association with another connective tissue disease (overlap syndrome), missing baseline HRCT or absence of clinical evaluation available at the time of the first HRCT diagnosing ILD.

Among 474 patients in our scleroderma database, 138 had SSc-ILD. Among them, 77 patients fulfilled the inclusion criteria. After exclusion of patient without clinical data or without HRCT available at baseline, we finally included 58 patients in our study (Flow Chart **Supplemental Figure 1**).

2- Clinical Data

Baseline was defined as the visit when the first HRCT 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 (6), 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, cardiac involvement, muscle involvement, arthritis, telangiectasia, scleroderma renal crisis at baseline or during follow-up,

gastroesophageal reflux symptoms, intestinal involvement, calcinosis, digital ulcer or pitting scars.

3- Biological Data

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

4- Echocardiography and Right Heart Catheterization

Left ventricular ejection fraction (LVEF) was recorded when available at baseline (41 patients of 58).

Precapillary pulmonary arterial hypertension (PAH) was defined by mean pulmonary artery pressure above 25 mmHg and pulmonary wedge pressure below 15 mmHg, at baseline or during follow-up. Nine patients underwent right heart catheterization.

5- Pulmonary Function Tests (PFTs)

All serial PFTs from baseline to the last visit, defined as the time of the last HRCT available, were recorded, including corrected DLCO, FVC and TLC, expressed in percentage of predicted value for age, gender, height, and hemoglobin for DLCO (34,35).

FVC was obtained by spirometry, TLC by plethysmography or helium dilution test, DLCO by single-breath nitrogen test.

6- High Resolution Computed Tomography (HRCT)

All HRCT available were blindly reviewed by two radiologists.

Six levels were analyzed: 1, origin of great vessels; 2, carina; 3, pulmonary venous confluence; 4, between levels 3 and 5; 5, 1 cm above the right hemi-diaphragm; and 6, 2 cm below the right hemi-diaphragm as described in (36) (**Supplemental Figure 2)**.

At each level, the following features were noted:

- the overall extent of ILD in % of lung parenchyma,
- the relative proportion of reticular pattern,
- the relative proportion of GGO,
- the coarseness of ILD (0: GGO alone, 1: fine intralobular fibrosis, 2: microcystic reticular pattern comprising air spaces smaller than or equal to 4 mm in diameter, 3: macrocystic reticular pattern comprising air spaces larger than 4 mm in diameter),
- the traction bronchiectasis score (0: none, 1: mild, 2: moderate, 3: severe),
- the extent of emphysema.

Then, we calculated:

- the overall extension of ILD by averaging the % of ILD of each level,
- the overall extension of reticulation by averaging the extent of reticulation at each level,
- the overall proportion of GGO by dividing the extent of GGO by the extent of ILD,

- the overall coarseness score by summing the scores at the six levels, adjusted proportionally to a six-level score for patients with no disease in one or several levels,
- the overall traction bronchiectasis score by summing the scores at the six levels, adjusted proportionally to a six-level score for patients with no disease in one or several levels,
- The overall extension of emphysema by averaging the extension of each level.

Radiologists gave a semi quantitative ILD grade on the whole scan (1: predominant GGO, 2: equal proportion of GGO and reticular pattern, 3: predominant reticular pattern).

Finally, ILD was classified using the staging system described by Goh *et al.*, as limited (below 20% of pulmonary parenchyma) or extensive (above 20% of pulmonary parenchyma). If indeterminate, ILD was classified as extensive or limited according to FVC, respectively below or above 70% (11).

Some examples of HRCT features can be seen in **Supplemental Figure 3**.

7- Statistical Analysis

All results of qualitative 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 evolution of ILD extension during the study period was analyzed using linear mixed model with random coefficients. This model is a generalization of the ANOVA for repeated measures. It is appropriate in situations when the number and the time of repeated measurements differ between the subjects and it allows handling the correlations between the repeated measurements. In addition, the random intercept and the random slope allow us to take into account the variability in the trajectories between the subjects and the fixed part of the model corresponds to the mean evolution. Normality of model residuals was checked with normal probability plot.

The association between each baseline factor and variation of ILD extension was studied using a mixed model with random coefficients (bivariate analyses). A multivariate analysis could not be performed due to the small sample size and the presence of missing data compared to the number of significant factors at the level of 0.05 in bivariate analyses.

Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

IV- Results

1- Baseline characteristics

We included 58 patients (67% of women) with ILD-SSc. Mean age at ILD diagnosis was 54.5 ± 14.9 years. Thirty-two patients had limited cutaneous SSc and 26 patients diffuse cutaneous SSc. ANA specificities were anti-topoisomerase 1 in 67.9 % of patients and anti-centromere in 17.9%.

Nine patients had right heart catheterization proven precapillary PAH at baseline or during follow-up.

PFTs performed at baseline showed a mean DLCO of 70.1 ± 25.5 % of predicted value (median 72.0 [54.0-81.0]%), a mean FVC of 96.4 ± 21.3% of predicted value (median 97.0 [83.0-111.0]%) and a mean TLC of 93.9 ± 18.6 % of predicted value (median 94.0 [83.0-107.3]%).

Concerning HRCT characteristics, mean ILD extension at baseline was 32.3 ± 28.7%, with a proportion of GGO of 89.5 ± 17.5% and a coarseness score of 3.4 ± 4%. ILD extension according to Goh *et al.* staging system was extensive in 48.5% of patients.

Details of baseline clinical, biological, functional and radiologic features at baseline are shown in **table 1 and table 2.**

At the end of follow-up, 18 (33.4%) patients had died. During follow up, 20 (34.5%) patients started immunosuppressive therapy.

Table 1. Clinical and biological characteristics at baseline.

	All patients	***Limited cutaneous SSc***	***Diffuse cutaneous SSc***	***p***
n (%)	58 (100)	32 (55.2)	26 (44.8)	
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	7.6 ± 11.4	7.9 ± 11.3	7.3 ± 11.6	NS
Disease duration since first non RP symptom, years	2.5 ± 3.1	2.4 ± 3.4	2.6 ± 2.9	NS
Smoker, n(%)	13 (23.2)	7(23.3)	6 (23.1)	NS
Dyspnea (NYHA), n (%)				
I	31 (53.4)	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	NS
LVEF < 60%, n (%)	5 (12.2)	2 (8.7)	3 (16.7)	NA
Precapillary PAH, n (%)	9 (15.5)	7 (21.9)	2 (7.7)	0.17
Crackles, n(%)	23 (40.3)	14 (45.2)	9 (34.6)	NS
Articular involvement, n (%)	18 (32.1)	9 (28.1)	9 (37.5)	NS
Muscular symptoms, n (%)	5 (9.3)	2 (6.4)	3 (13.0)	NA
SRC (at baseline or during follow-up), n (%)	2 (3.4)	0	2 (7.7)	NA
GERD, n (%)	32 (55.2)	17 (53.1)	15 (57.7)	NS
Intestinal involvement, n (%)	9 (17.6)	6 (23.1)	3 (12.0)	NS
Calcinosis, n (%)	4 (7.7)	3 (10.3)	1 (4.3)	NA
Telangiectasia, n (%)	19 (57.6)	12 (57.1)	7 (58.3)	NS
Digital ulcer (active or past history), n (%)	19 (32.8)	7 (21.9)	12 (46.1)	0.05
Hb, g/dL	13.32 ± 1.54	13.1 ±1.4	13.6 ± 1.7	0.06
CRP, mg/L	4.69 ± 4.43	3.6 ± 1.8	5.9 ± 6.0	0.07
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
RNAIII, n (%)	0	0	0	NA
Other antibodies, n (%)	4 (7.1)	2 (6.4)	2 (8.0)	NA

SSc: systemic sclerosis, ANA: antinuclear antibodies, ACA: anti-centromere antibodies, SCL70: anti-toposiomerase I antibodies, RNAIII: anti-RNA polymerase III antibodies, ILD: interstitial lung disease, RP: Raynaud's phenomenon, LVEF: left ventricular ejection fraction, PAH: pulmonary arterial hypertension, SRC: scleroderma renal crisis, GERD: gastroesophageal reflux disease, Hb: hemoglobin, CRP: C reactive protein, NS: p>0.2, NA: not applicable.

Table 2. ILD characteristics at baseline

		All patients	***Limited cutaneous SSc***	***Diffuse cutaneous SSc***	***p***
PFT, % of predicted value					
DLCO, %		70.1 ± 25.5	71.0 ± 21.4	69.1 ± 29.3	0.12
DLCO/VA, %		72.2 ± 17.3	74.2 ± 16.6	69.9 ± 18.1	0.09
FVC, %		96.4 ± 21.3	98.9 ± 21.6	93.8 ± 20.9	NS
TLC, %		93.9 ± 18.6	96.7 ± 19.1	90.1 ± 17.7	0.19
HRCT					
ILD extension (% of parenchyma)		32.3 ±28.7	32.5 ± 30.7	32.7 ± 26.1	NS
Proportion of GGO (% of ILD)		89.5 ± 17.5	87.8 ± 17.9	91.6 ± 16.6	NS
Extension of reticular pattern (% of parenchyma)		5.1± 9.9	5.4 ± 9.1	4.7 ± 10.9	NS
Coarseness score		3.4 ± 4.0	3.4 ± 3.3	3.5 ± 4.8	NS
Global score of bronchiectasis		3.6 ± 4.7	4.7 ± 4.9	2.3 ± 4.1	0.054
Extensive ILD (Goh et al. staging system), n (%)		28 (48.5)	15 (46.9)	13 (50.0)	NS
ILD grade, n (%)	***1***	44 (76.4)	23 (71.9)	21 (80.8)	
	2	10 (16.7)	7 (21.9)	3 (11.5)	NA
	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

SSc: systemic sclerosis, PFT: pulmonary function test, DLCO: diffusing capacity of the lung for carbon monoxide, DLCO/VA: transfer coefficient for the diffusion of CO, FVC: forced vital capacity, TLC: total lung capacity, HRCT: high resolution computed tomography, ILD: interstitial lung disease, GGO: ground glass opacification, NS: p>0.2, NA: not applicable.

2- Factors associated with ILD extension at baseline

In bivariate analysis, we found that a greater ILD extension on HRCT at baseline was associated with the presence of lung crackles, lower PFT parameters (DLCO, DLCO/VA, TLC, FVC), and HRCT characteristics such as a lower proportion of GGO and a higher bronchiectasis score. Presence of PAH was also associated with a higher ILD extension at baseline (**tables 3 and 4).**

Table 3. Bivariate analysis of clinical and biological parameters associated with baseline ILD extension on HRCT.

		Mean baseline ILD extension, % of parenchyma	SE	p
Gender	men	35.44	7.72	NS
	women	31.23	4.42	
SSc subtype	limited	32.50	7.27	NS
	diffuse	32.54	5.41	
Smoker	no	29.79	8.42	0.180
	yes	41.16	7.38	
Age at ILD diagnosis	< 54	29.59	7.14	NS
	≥ 54	35.72	5.05	
Duration since RP, years	< 4	30.93	7.24	NS
	≥ 4	33.33	4.92	
Duration since FNRP symptom, years	= 0	33.85	8.16	NS
	≥ 1	32.95	4.49	
Dyspnea	no	28.09	7.10	0.186
	yes	37.57	5.18	
PAH	no	27.75	8.28	**0.0007**
	yes	59.60	9.01	
Crackles	no	25.11	7.01	**0.009**
	yes	43.77	5.40	
Arthritis or synovitis	no	34.12	6.48	NS
	yes	31.87	7.88	
GERD	no	30.56	7.22	NS
	yes	34.35	4.84	
Intestinal involvment	no	31.32	10.33	NS
	yes	32.80	9.37	
Digital ulcer (actual or past history)	no	32.48	7.66	NS
	yes	33.12	6.28	
Laboratory tests				
Hb, g/dl	< 13.4	39.49	7.62	0.107
	≥ 13.4	27.08	5.34	
CRP, mg/dl	≤ 3	32.16	8.20	NS
	> 3	35.64	6.54	
Anticentromere antibodies	no	34.50	9.68	NS
	yes	29.63	8.78	
Anti-topoisomerase 1 antibodies	no	29.99	7.89	NS
	yes	35.56	4.46	

ILD: interstitial lung disease, SSc: systemic sclerosis, RP: Raynaud's phenomenon, FNRP: first non-Raynaud's phenomenon, PAH: pulmonary arterial hypertension, GERD: gastroesophageal reflux disease, Hb: hemoglobin, SE: standard error, NS: $p<0.2$.

Table 4. Bivariate analysis of PFT and HRCT parameters associated with baseline ILD extension on HRCT.

		Mean baseline ILD extension, % of parenchyma	SE	p
HRCT				
ILD extension according to Goh *et al*. staging system	limited extensive	12.19 54.47	4.43 3.18	0.013
Baseline ILD extension	< 30% > 30%	13.49 56.06	4.43 3.28	**<0.0001**
Baseline ILD extension	< 20% > 20%	11.12 52.5	4.62 3.19	**<0.0001**
ILD grade	1 2 3	25.84 53.58 56.96	13.01 14.73 12.47	**0.02**
Coarseness score	0 > 0	24.12 41.53	6.78 4.87	**0.012**
Global score of bronchiectasis	0 > 0	42.98 46.22	6.60 5.06	**0.0007**
Proportion of GGO	< 100 % 100 %	42.56 23.27	6.69 4.65	**0.005**
PFT, % of predicted value				
DLCO	< 70% > 70%	47.01 19.10	6.60 4.52	**<0.0001**
DLCO/VA	≤ 74% > 74%	43.92 22.21	8.04 5.88	**0.009**
FVC	< 97% > 97%	38.40 26.17	7.33 5.32	0.099
TLC	< 94 % > 94 %	47.67 16.21	6.49 4.76	**<0.001**

ILD: interstitial lung disease, HRCT: high resolution computed tomography, GGO: ground glass opacification, PFT: pulmonary function test, DLCO: diffusing capacity of the lung for carbon monoxide, DLCO/VA: transfer coefficient for the diffusion of CO, FVC: forced vital capacity, TLC: total lung capacity, SE: standard error, NS: p>0.2.

3- Evolution on HRCT

Patients underwent a median number of three HRCT (range 2-10), during a mean follow-up of 5.3 ± 4.9 years.

The mean progression of ILD extension was 0.92% ± 0.36 per year (p=0.018) **(Figure 1)**.

We were not able to modelize the evolution of proportion of GGO and reticular pattern extension using this statistical model because these parameters did not follow a normal distribution.

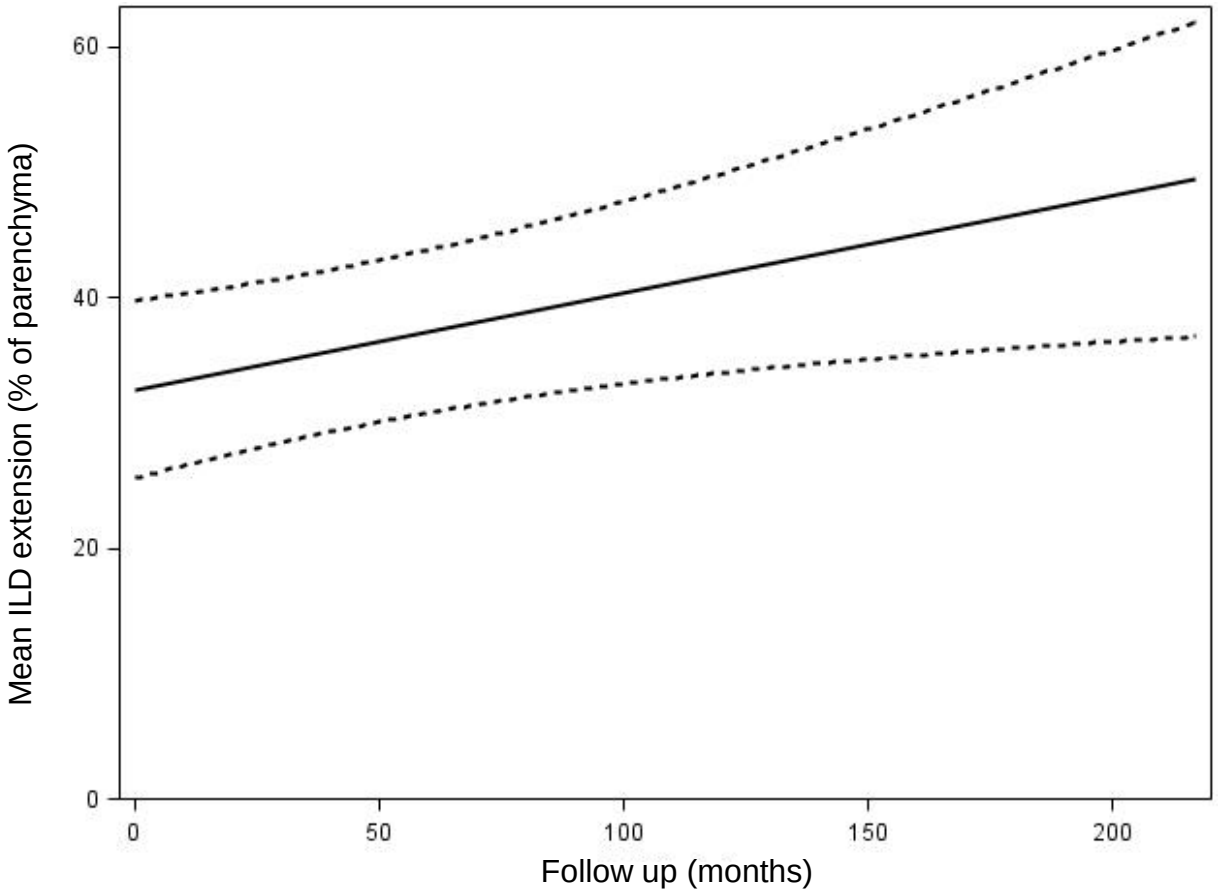

Figure 1. Mean progression of ILD extension.

The solid line corresponds to the mean ILD extension, the dashed lines to the 95% confidence interval.

4- Baseline parameters associated with the progression of ILD extension

Next, we assessed the correlation between baseline characteristics and progression of ILD extension on HRCT in bivariate analysis.

We found that male sex, diffuse cutaneous SSc, presence of anti-topoisomerase 1 antibodies, absence of dyspnea, hemoglobin higher than 13.4 g/dL (median) and a higher DLCO at baseline were associated with a faster progression of ILD extension.

Among HRCT characteristics at baseline, a limited ILD according to Goh *et al*. staging system, an ILD extension lower than 20%, a coarseness score of 0, the absence of bronchiectasis and a proportion of GGO of 100% were associated with a faster progression of ILD extension **(Tables 5, 6 and Figure 2)**.

Conversely, neither age at diagnosis, disease duration, PAH, GERD, digital ulcer, CRP, TLC, FVC, nor ILD global score at baseline were associated with any change in the evolution of ILD extension.

Table 5. Bivariate analysis of clinical and biological parameters at baseline associated with the progression of ILD extension over time.

		Mean progression of ILD extension (%/year)	SE	p
Gender	men women	2.52 0.24	0.96 0.48	**0.013**
SSc subtype	limited diffuse	0.12 1.92	0.84 0.60	**0.029**
Smoker	no yes	0.84 1.44	1.08 1.08	NS
Age at ILD diagnosis, years	< 54 ≥ 54	0.96 0.84	0.72 0.48	NS
Duration since RP, years	< 4 ≥ 4	1.32 0.60	0.84 0.48	NS
Duration since FNRP symptom, years	= 0 ≥ 1	0.60 0.96	0.84 0.60	NS
Dyspnea	no yes	1.80 0.24	0.72 0.48	**0.044**
PAH	no yes	1.08 -0.12	0.96 0.96	NS
Crackles	no yes	1.80 0.36	0.72 0.60	**0.082**
Arthritis or synovitis	no yes	0.84 1.08	0.72 0.60	NS
GERD	no yes	0.72 1.08	0.84 0.48	NS
Intestinal involvement	no yes	1.32 0.60	1.08 1.08	NS
Digital ulcer (actual or past history)	no yes	1.08 0.48	0.84 0.72	NS
Laboratory tests				
Hb, g/dl	< 13,4 ≥ 13,4	-0.01 2.04	0.96 0.60	**0.029**
CRP, mg/dl	≤ 3 > 3	1.44 0.72	0.96 0.72	NS
Anti-centromere antibodies	no yes	1.20 -1.08	1.08 1.08	**0.052**
Anti-topoisomerase 1 antibodies	no yes	-0.72 1.32	0.96 0.48	**0.034**

ILD: interstitial lung disease, SSc: systemic sclerosis, RP: Raynaud's phenomenon, FNRP: first non-Raynaud's phenomenon symptom, PAH: pulmonary arterial hypertension, GERD: gastroesophageal reflux disease, Hb: hemoglobin, CRP: C reactive protein, SE: standard error, NS: p>0.2.

Table 6. Bivariate analysis of baseline PFT and HRCT parameters associated with the progression of ILD extension over time.

		Mean progression of ILD extension (%/year)	SE	p
HRCT				
ILD extension according to Goh *et al* staging system	limited extensive	1.80 0	0.72 0.60	**0.013**
ILD extension	< 30% > 30%	1.92 0	0.72 0.60	**0.013**
ILD extension	< 20% > 20%	1.80 0.12	0.72 0.60	**0.022**
ILD grade	1 2 3	1.20 -0.60 0.48	1.44 1.92 1.32	NS
Coarseness score	0 > 0	2.04 0.24	0.72 0.48	**0.008**
Global score of bronchiectasis	0 > 0	0.72 -0.12	0.72 0.60	**0.008**
Proportion of GGO	< 100 % 100%	0.36 1.80	0.72 0.48	**0.029**
PFT, % of predicted value				
DLCO	< 60% > 60%	-0.72 1.68	0.96 0.36	**0.011**
DLCO/VA	≤ 74% > 74%	0.72 1.44	0.96 0.72	NS
FVC	< 97% > 97%	1.2 1.08	0.84 0.48	NS
TLC	< 94 % > 94 %	0.48 1.44	0.84 0.48	NS

ILD: interstitial lung disease, HRCT: high resolution computed tomography, GGO: ground glass opacification, PFT: pulmonary function test, DLCO: diffusing capacity of the lung for carbon monoxide, DLCO/VA: transfer coefficient for the diffusion of CO, FVC: forced vital capacity, TLC: total lung capacity, GGO: ground glass opacification, SE: standard error, NS: p>0.2.

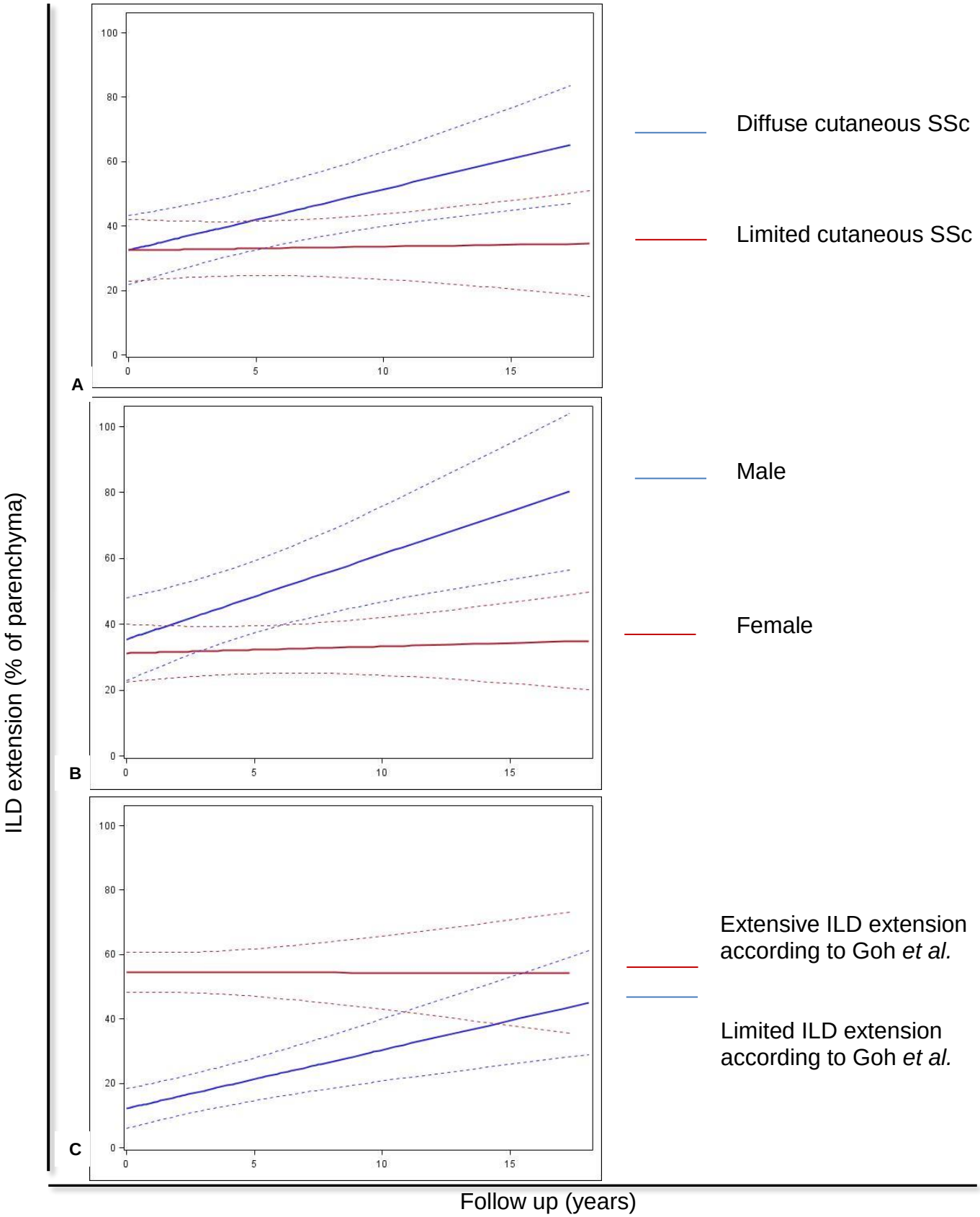

Figure 2. Mean evolution of ILD extension according to some illustrative baseline parameters, using the linear mixed model with random coefficients. The solid line corresponds to the mean, the dashed lines to the 95% confidence interval. **A:** Patients with a diffuse cutaneous SSc had a faster progression of ILD extension than patients with limited cutaneous SSc in bivariate analysis (1.92 ± 0.60% vs 0.12 ± 0.84% per year, p=0.029). **B:** Male sex patients had a faster progression of ILD extension than female patients in bivariate analysis (2.52 ± 0.96% vs 0.24 ± 0.48 % per year, p=0.013). **C:** 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.* (1.80 ± 0.72% vs 0.0 ± 0.60 % per year, p=0.013).

5- Evolution of PFTs and correlation with the progression of ILD extension

a. Evolution of PFTs (figure 3)

We next assessed the evolution of PFT parameters. The median number of PFTs performed during follow-up was 5 (range 1-16). During follow up, mean DLCO decline was -2.00 ± 0.36% per year (p<0.001). Mean FVC decline was -0.43 ± 0.24% per year (p=0.048). Mean TLC decline was -0.85 ± 0.24% per year (p=0.001). DLCO/ VA did not change significantly during follow up (-0.12 ± 0.16% per year (p=0.779)).

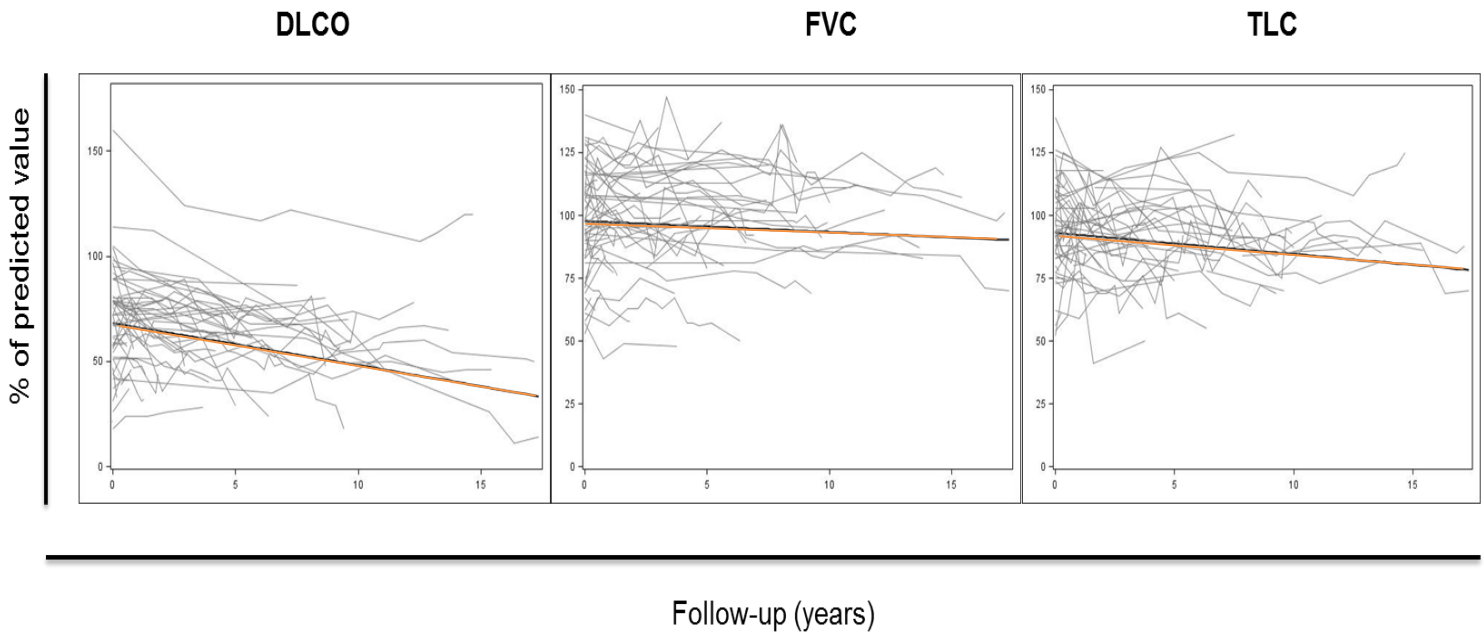

Figure 3. Individual trajectories of the 58 patients (in black) and mean evolution (in orange) of diffusing capacity of the lung for carbon monoxide (DLCO), forced vital capacity (FVC) and total lung capacity (TLC) using the linear mixed model with random coefficient. Mean DLCO decline was -2.00 ± 0.36% per year (p<0.001). Mean FVC decline was -0.43 ± 0.24% per year (p=0.048). Mean TLC decline was -0.85 ± 0.24% per year (p=0.001).

b. Correlation between the evolution of PFTs and the progression of ILD extension

We assessed the correlation between the progression of ILD extension on HRCT and the decline of PFT parameters over time. There was a significant correlation between the progression of ILD extension on HRCT and the decline of DLCO during follow up. For 1% progression of ILD extension on HRCT, DLCO decreases of 0.45% in a year. There was a trend towards a correlation between the progression of ILD extension on HRCT and the decline of FVC during follow-up, but it did not reach significance **(Table 7).**

Table 7. Correlation between the evolution of PFT parameters and the progression of ILD extension over time.

	Progression of ILD extension (% per year)	**SE**	**p**
DLCO	-2.2	0.5	**0.014**
DLCO/VA	-3.9	0.4	0.083
FVC	-0.5	0.2	0.085

ILD: interstitial lung disease, DLCO: diffusing capacity of the lung for carbon monoxide, DLCO/VA: transfer coefficient for the diffusion of carbon monoxide, FVC: forced vital capacity, SE: standard error.

V- Discussion

The main results of our study were as follow: 1) The mean progression of SSc-ILD extension on HRCT was 0.92 ± 0.36% per year (p=0.018) in our population; 2) We identified several clinical and paraclinical baseline factors associated with a faster progression of SSc-ILD extension over time: male gender, diffuse cutaneous SSc, presence of anti-topoisomerase 1 antibodies, absence of dyspnea, hemoglobin higher than 13.4 g/dL (median), higher DLCO at baseline; 3) We identified several baseline HRCT characteristics associated with a faster progression of SSc-ILD extension over time: limited ILD according to Goh *et al.* staging system, a coarseness score of 0, the absence of bronchiectasis and a proportion of ground glass opacities of 100%; 4) There was a correlation between the progression of ILD extension over time and the decline in DLCO. Conversely, there was only a non-significant trend for the association between the progression of ILD extension over time and the decline in FVC.

Though we found an ILD extension at baseline quite high, our patients had a slight functional impairment as indicated by a high FVC and DLCO at baseline compared to other studies **(table 8).** Using a linear mixed model with random coefficients, we found a significant progression of ILD extension on HRCT during follow up, with a mean rate of 0.92 ± 0.36% per year. This is consistent with the placebo group of SLS with a progression of ILD extension of 2.2% at 12 months (37), and with the study of Hoffman Vold *et al*., which found an annual ILD progression rate of 0.5 ± 2.2% (33). We were not able to analyze by the same statistical approach the variation of HRCT patterns over time because of the non-normal distribution of these parameters. Similarly to others, we showed previously that the HRCT pattern evolution in SSc-ILD was characterized by a decrease in GGO and an increase in honeycombing (14,37).

Some baseline characteristics were associated with a faster progression of SSc-ILD extension on HRCT over time. Some may have been anticipated, such as male gender, diffuse cutaneous SSc, and the presence of anti-topoisomerase 1 antibodies. Male gender has already been described as being associated with an ILD extension of more than 20% (33) and with end stage lung disease (38). Moreover, several studies found that male gender is associated with mortality in SSc-ILD (11,18) and time to decline in DLCO (11). However, the precise impact of male gender on HRCT evolution was unknown. Anti-topoisomerase 1 antibodies are known as a predictive factor for the presence of ILD in SSc (23), but to our knowledge it is the first time that they are described as associated with a faster progression of SSc-ILD extension. Similarly, the diffuse type of scleroderma is known to be a risk factor for developing ILD (24) and was described as a mortality factor in SSc-ILD (39), but it had not yet been described as a worsening factor of ILD extension. Gilson *et al.* showed previously that the diffuse subtype of SSc was independently associated with a decrease in FVC over time (32), but their study concerned a population composed of patients with and without ILD at baseline. On the whole, data are contradictory in the literature (40).

Other parameters associated with a faster progression of SSc-ILD extension on HRCT over time were more surprising, such as the absence of dyspnea and of lung crackles at baseline. Only one study to our knowledge found that a lower frequency of lung crackles was associated with a progression of ILD on HRTC (14). It must be highlighted that patients without dyspnea and patients without lung crackles have a lower extension of ILD at baseline but a faster evolution. This could be interpreted thus: the least severe patients at baseline progress the most over time. The same explanation can be proposed for DLCO above 60% at baseline being associated with a faster progression of SSc-ILD extension on HRCT over time. Conversely, neither FVC nor

TLC at baseline were associated with the evolution of ILD extension. Concerning HRCT baseline characteristics, we also found that a less extensive and less severe ILD on baseline HRCT shown by a limited ILD according to Goh *et al.* staging system, the absence of bronchiectasis, a coarseness score of zero, a proportion of ground glass opacities of 100% were associated with a faster progression of ILD extension over time. Our results could be interpreted as contradictory with other studies, which usually suggest that a more severe ILD at baseline (either on extension or on the severity of ILD) is associated with a bad outcome. In fact, there is no discrepancy as the different studies do not assess the same outcome parameters **(see table 8).** For example, Moore *et al.* found that an extensive ILD according to Goh *et al.* staging system on HRCT at baseline was associated with death, need for home oxygen or lung transplantation. (41). Goh *et al.* have shown that an extensive ILD on baseline HRCT was associated with a faster decline of FVC and DLCO as defined by a drop of 10% and 15% respectively (11). In the placebo group of SLS, with a follow-up limited to one year, there was a greater decline of FVC when ILD score was more severe on baseline HRCT (27). However, these studies defined the worsening of ILD on PFT or clinical parameters. Moreover, they did not assess whether an extensive ILD was associated or not with a faster progression of ILD extension on serial HRCT as in our study. Indeed, only a few studies focused on ILD-SSc progression on HRCT. Hoffmann-Vold *et al.* recently found in 197 patients with SSc-ILD that a lower FVC and DCLO at baseline were associated with ILD extension of more than 20% on HRCT at the end of follow-up. However, a final ILD extension of more than 20% is not synonymous with a faster progression of ILD extension over time as, for example, some patients had already an ILD extension of more than 20% at baseline, or might have had a small and slow progression of ILD leading them just above the cut-off of 20% (33). Wangkaew *et*

al. studied the evolution of ILD on HRCT but did not evaluated the correlation with baseline HRCT parameters (42).

In our study, FVC declined very mildly by 0.43 ± 0.24% per year while DLCO had a significant and higher decline of 2.00 ± 0.36% per year. The small decline in FVC is in line with other studies, some of them even finding a stability of FVC over time (18,40). We found a significant correlation between the progression of ILD extension on HRCT and the decline of DLCO (% predicted) during follow up, but not with FVC, as reported by Wangkaew *et al* (42). Gilson *et al.* found a correlation between the worsening of ILD on HRCT and the decline of FVC, but these results concerned a small number of patients. Moreover, in the 15 patients with a worsening of FVC, there was a worsening of HRCT in only eight cases (32). Kim *et al*. found a correlation between the change in computed fibrosis score and the change of FVC at twelve months in a group of patients from SLS. Nevertheless, this result concerns selected patients as part of a clinical trial, and can therefore not be applied to an unselected population. Moreover, the follow-up was quite short, of only one year, and FVC worsening was defined only with the baseline and twelve month values, not taking into account possible variations of this parameter (37) **(table 8).** Altogether, our results suggest that DLCO could better reflect ILD progression than FVC.

Our study has some limitations, the main one being its retrospective design with a rather small sample size. The sample size is explained as we needed patients with ILD-SSc who underwent serial HRCT, which limited the number of available patients. This study has some strengths: all HRCT were blindly reviewed by two experienced radiologists specialized in lung disease. The statistical method is original and robust and allows to modelize the evolution of ILD, taking into account the variability of the

interval between two HRCT. The population of this study is very well phenotyped, and we were able to evaluate not only clinical characteristics associated with ILD progression, but also PFT and HRCT data with a long follow-up.

In conclusion, in this study analyzing the progression of SSc-ILD on serial HRCT of 58 SSc patients, we found an annual progression of ILD extension of 0.92 ± 0.36%. Patients with a less severe and less extensive ILD at baseline were more likely to experience a faster progression of ILD extension on serial HRCT during follow-up. Male gender, diffuse cutaneous SSc and anti-topoisomerase 1 antibody were also associated with a faster progression of ILD extension. Finally, there was a correlation between the progression of ILD extension and the decline of DLCO but not FVC over time. Our study helps to define the profile of patients who are going to experience a progression of ILD on HRCT.

Table 8. Comparison of recent studies evaluating the evolution of SSc-ILD.

	Goh *et al.* (11)	**Hoffman-Vold *et al.*** (33)	**Le Gouellec *et al.*** (40)	**Wangkaew *et al.*** (42)	**Kim *et al.*** (37) ****SLS population*** (27)	**Moore *et al.*** (41)	**Present study**
Patients selection	215 patients with HRCT confirmed ILD	65% of 305 patients had ILD at baseline	75 patients 1 HRCT, at least 2 PFTs	31 patients Early disease <3years, 30% immuno-suppressant	83 patients, from SLS	172 patients with HRCT confirmed ILD	58 HRCT proven ILD At least 2 HRCT
Exclusion criteria	Baseline investigations separated by more than 90 days, no follow-up,	-	HRCT or PFT missing at baseline	Overlap	DLCO< 30%, smoking, significant HTAP, FVC < 45%	Absence of baseline HRCT	Overlap, absence of clinical evaluation available at baseline
Outcome parameter	Time to decline in PFT (≥ 10% in FVC, ≥ 15% in DLco), progression free survival	No lung fibrosis and >20% fibrosis at follow up	Evolution of FVC and DLCO	Changes in computer-based HRCT scores	12-months changes in computer aided score	Death, supplemental oxygen, lung transplantation	Progression of ILD extension on serial HRCT
Age, years	49.1 ± 13	48 ± 15.0	52.0 ± 15.8	52.3 ± 8.8	47.9 ± 1.0*	55.5 ± 13.0	54.5 ± 14.9
Disease duration, years	-	4.2 ± 4.5	2.8 ± 3.8	1.0 ± 0.6	3.2 ± 0.3*	10.5 ± 10.1	2.5 ± 3.1
Mean Follow up, years	7.4	3.1	6.4 ± 4.2	-	1	3.5 ± 2.9	5.3 ± 4.9
ILD extension (% of parenchyma)	13,5 (1.0-84.0)	-	12,9 (2.1-86.2)	Score not comparable	-	-	24.2 (8.3-54.1)
	-	6.8 ± 13	20.9 ± 18.8				32.3 ± 28.7
Extension of reticular pattern (% of parenchyma)	6,5 (0-56,7)	-	2,4 (0-42) 6.0 ± 9.5	-	-	-	0.0 (0.0-4.7) 5.1 ± 9.9
Proportion of GGO (% of ILD)	49,0 ± 28,5	-	74,4 ± 27,7	-	-	-	89.5 ± 17.5
Coarseness score	5,5 (0-13,3)	-	3,60 (0-12) 3.2 ± 2.7	-	-	-	0.0 (0.0-6.0) 3.4 ± 4
Extensive ILD according to Goh *et al., %*	-	-	24%	-	-	30.9%	48.5%
Baseline FVC, %	78,7 ± 21,4	92.7 ± 20.9	90,2 ± 19,8	69.0 ± 15.9	68.1 ± 1.0*	84.1 ± 17.4	96.4 ± 21.3
Baseline DLCO, %	55,1 ± 16,8	66.5 ± 20.8	67,2 ± 23,8	-	47.2 ± 1.1*	56.2 ± 15.2	70.1 ± 25.5

SSc: systemic sclerosis, ILD: interstitial lung disease, HRCT: high resolution computed tomography, DLCO: diffusing capacity of the lung for carbon monoxide, FVC: forced vital capacity

VI- Conclusion

Les principaux résultats de notre étude sont les suivants : 1) La progression moyenne de l'étendue de la PID-SSc était de 0.92 ± 0.36% par an (p=0.018). 2) Nous avons identifié plusieurs paramètres initiaux associés à une progression plus rapide de la PID-SSc au cours du temps : le genre masculin, la forme cutanée diffuse de la SSc, la présence d'anticorps anti-SCL70, l'absence de dyspnée, l'hémoglobine supérieure à une médiane de 13.4 g/dl, la DLCO plus élevée initialement. 3) Nous avons identifié plusieurs caractéristiques scanographiques initiales associées à une progression plus rapide de la PID-SSc au cours du temps : une PID limitée selon la classification de Goh *et al*., un score de sévérité nul, l'absence de bronchectasies et une proportion de verre dépoli représentant 100% de la PID. 4) Il existait une corrélation entre la progression de l'étendue de la PID en TDM au cours du temps et le déclin de la DLCO. En revanche, il n'y avait qu'une tendance non significative concernant l'association entre la progression de l'étendue de la PID en TDM au cours du temps et le déclin de la CVF.

Malgré les limites inhérentes aux études rétrospectives, grâce à une relecture en aveugle de l'ensemble des TDM disponibles par des radiologues expérimentés spécialisés dans la PID, et grâce à l'utilisation d'une méthode statistique robuste et adaptée, nous avons pu évaluer l'évolution scanographique de la PID et déterminer les facteurs cliniques, fonctionnels et scanographiques associés à la progression de la PID sur une longue durée de suivi.

Notre étude aide ainsi à définir le profil de patients à risque de progression scanographique de la PID-SSc.

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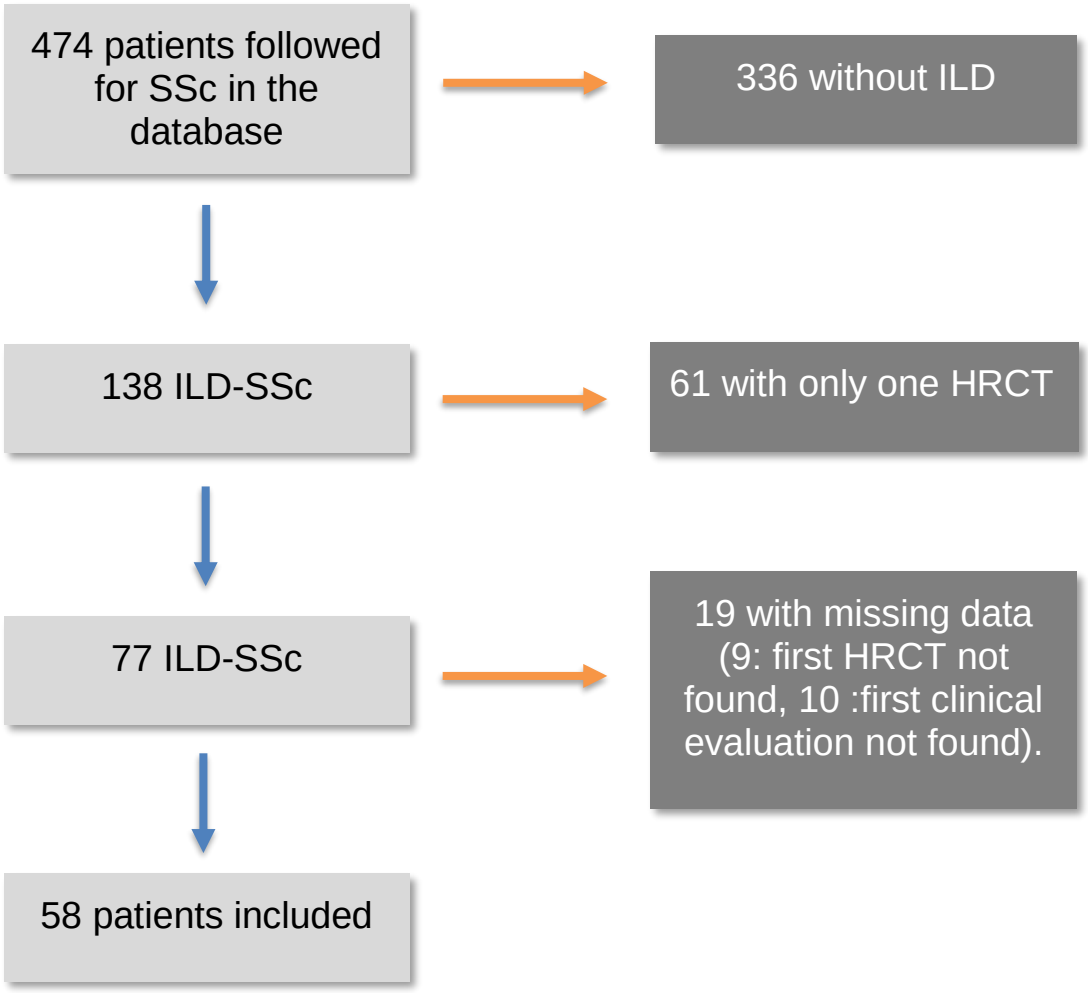
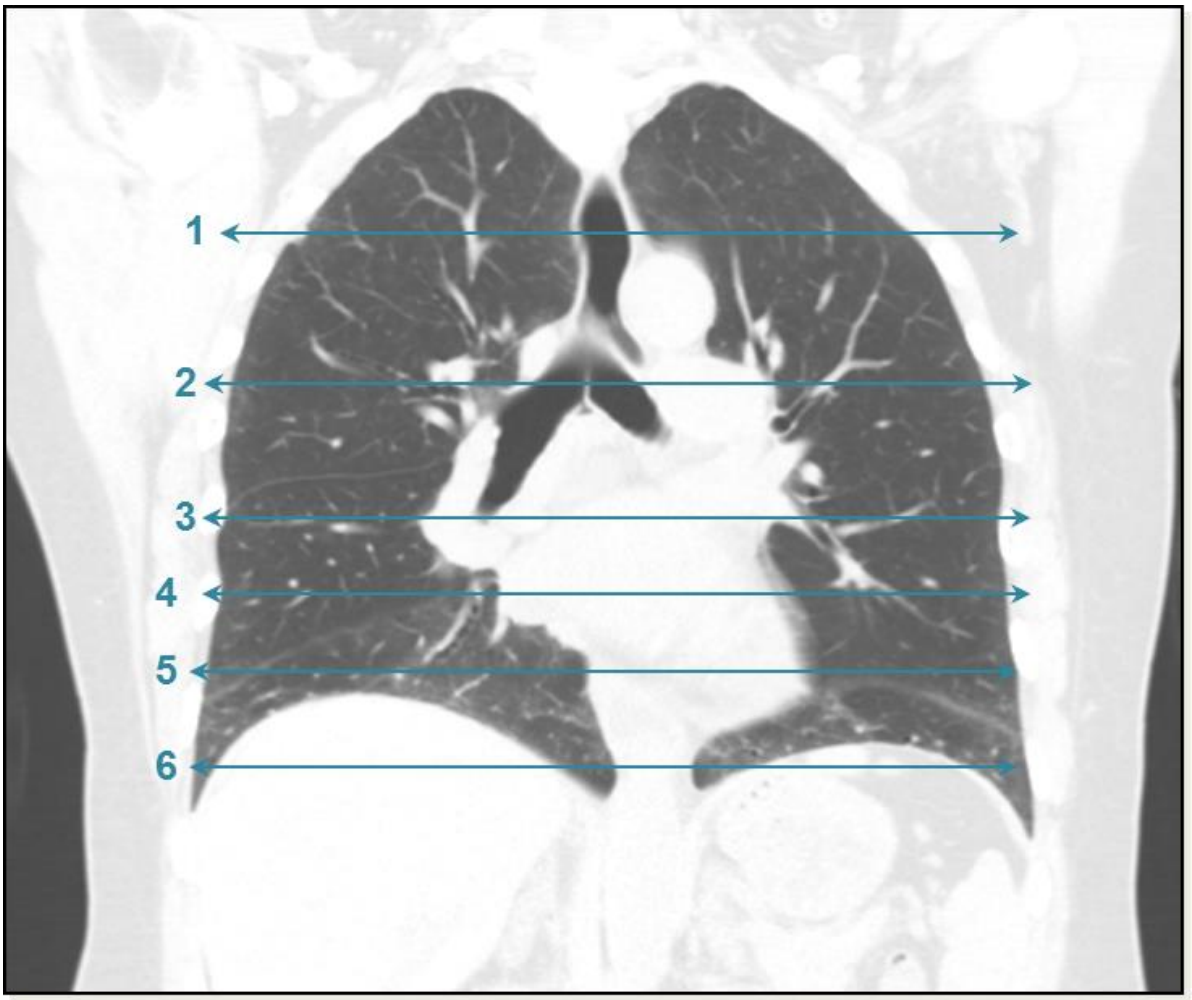
Annexes

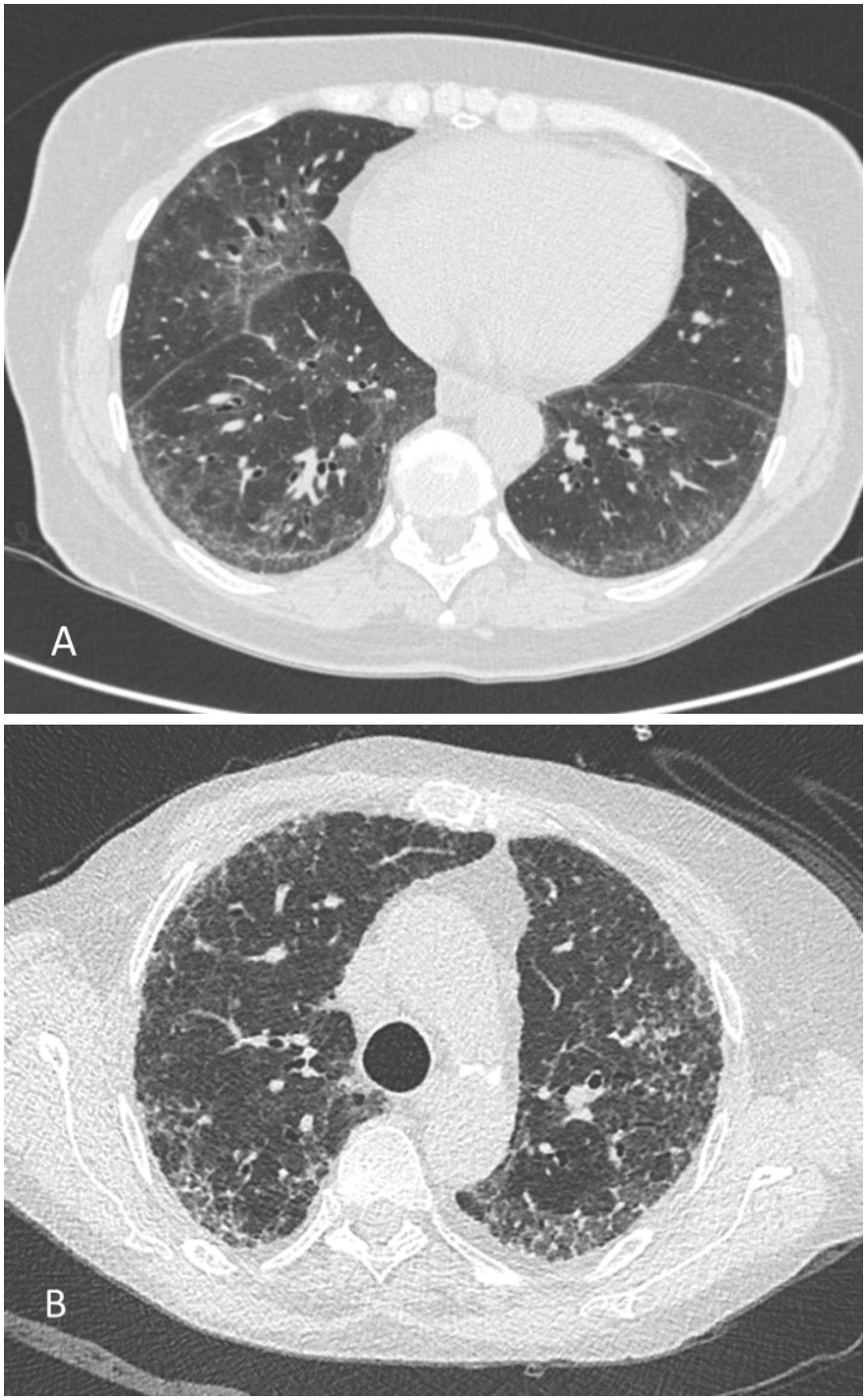


Supplemental Figure 1. Flow chart

SSc: systemic sclerosis, ILD: interstitial lung disease, HRCT: high resolution computed tomography.



Supplemental Figure 2. Six levels studied on high resolution computed tomography (HRCT): 1, origin of great vessels; 2, carina; 3, pulmonary venous confluence; 4, between levels 3 and 5; 5, 1 cm above the right hemi-diaphragm; and 6, 2 cm below the right hemi-diaphragm.



Supplemental Figure 3. Examples of high resolution computed tomography (HRCT) features in patients with SSC-ILD. **A:** 54-year-old woman with limited cutaneous SSc. Axial image of HRCT obtained in the basal region showing ground-glass opacifications distributed all over the parenchyma, with higher density in the peripheral areas of the medium and lowers lung lobes. There are some traction bronchiectasis in the medium lobe, associated with thin cortical reticular pattern and a loss of volume of the two lower lobes, suggesting the presence of pulmonary fibrosis. **B**: 79-year-old woman with limited cutaneous SSc. Axial image of HRCT obtained in the aortic arch region showing ground-glass opacifications distributed all over the parenchyma associated with intralobular reticular pattern and microcysts suggesting the presence of pulmonary fibrosis.

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Date de Soutenance : 18 septembre 2017

Titre de la Thèse : Facteurs prédictifs d'évolution scanographique de la Pneumopathie Interstitielle Diffuse liée à la Sclérodermie Systémique

Thèse - Médecine - Lille 2017

Cadre de classement : *Médecine*

DES + spécialité : *Médecine Interne*

Mots-clés : Sclérodermie Systémique, Pneumopathie Interstitielle Diffuse, Facteurs Pronostics, Epreuves Fonctionnelles Respiratoires, Scanner Thoracique

Résumé : Introduction : La pneumopathie interstitielle diffuse (PID) est une des causes majeures de morbi-mortalité dans la sclérodermie systémique (SSc). Alors que les facteurs associés à l'apparition de la PID dans la SSc (PID-SSc) sont identifiés, ceux associés à son aggravation sont moins décrits et les études évaluant l'évolution en tomodensitométrie (TDM) de la PID-SSc sont rares. Il est pourtant nécessaire d'identifier les patients à risque d'aggravation dans un but thérapeutique. Ainsi, les objectifs de notre étude sont de décrire l'évolution scanographique de la PID-SSc, d'identifier les facteurs de risques initiaux d'aggravation de cette PID, et de déterminer si l'évolution TDM est corrélée à l'évolution des épreuves fonctionnelles respiratoires (EFR). **Patients et méthodes** : Nous avons inclus 58 patients avec une PID-SSc, ayant au moins deux TDM, et avons recueillis les données clinicobiologiques, fonctionnelles et scanographique au diagnostic, ainsi que l'ensemble des EFR et des TDM au cours du suivi. Les caractéristiques de la PID ont été évaluées sur 6 niveaux de coupe pour chaque TDM. L'évolution des EFR et des scanners a été analysée à l'aide d'un modèle linéaire mixte à coefficients aléatoires. **Résultats :** L'extension moyenne de la PID au diagnostic était de 32.3 ± 28.7%. Nous avons mis en évidence une progression moyenne de 0.92 ± 0.36% par an au cours d'un suivi moyen de 5.3 ± 4.9 ans. Le genre masculin, la présence d'anticorps anti-SCL70, la forme cutanée diffuse de la SSc étaient associés à une progression plus rapide de la PID. Une PID limitée selon Goh *et al*., une moindre extension initiale, un score de sévérité nul, l'absence de bronchectasie, la présence de 100% de verre dépoli sur la TDM initiale étaient associés à une progression plus rapide de la PID. Nous avons également trouvé un déclin de DLCO, de CVF et de CPT au cours du suivi, avec une corrélation entre la progression scanographique de l'ILD et le déclin de DLCO, mais pas avec l'évolution de la CVF. **En conclusion**, nos patients présentaient un PID étendue au diagnostic mais étaient peu altérés sur le plan fonctionnel. Les patients les moins sévères au diagnostic étaient plus à risque de voir leur PID progresser au cours du suivi. Il s'agit de la première étude qui rapporte la forme cutanée diffuse et les anticorps anti-SCL70 comme facteurs de risque d'aggravation de la PID. Notre étude aide à définir le profil de patients à risque de progression scanographique de la PID.

Composition du Jury :

Président : Monsieur le Professeur Hatron

Assesseurs : Madame le Professeur Martine REMY-JARDIN, Monsieur le Professeur Eric HACHULLA, Monsieur le Professeur David LAUNAY, Monsieur le Docteur Thierry PEREZ, Madame le Docteur Noémie LE GOUELLEC (Directrice de Thèse)