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SEMINARS IN ARTHRITIS AND RHEUMATISM

Original Clinical Research Study

Association of silica exposure with chest HRCT and clinical characteristics in Systemic Sclerosis

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Running heading : Silica and HRCT findings in SSc

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ABSTRACT

Context: Thoracic lymphadenopathy (LA) has been identified as a key prognostic factor in interstitial lung disease (ILD) of all-cause. Crystalline silica is a risk factor of systemic sclerosis (SSc). The association of a history of crystalline silica exposure with chest high-resolution computed tomography (HRCT) features and thoracic LA are still to be determined in SSc patients.

Objectives : We performed an observational study to assess the association of lifetime exposure to silica, with chest HRCT characteristics in a population of SSc patients fulfilling the 2013 ACR/EULAR classification criteria for SSc.

Methods: A specific questionnaire based on a multidisciplinary approach was used to assess occupational and non-occupational exposure to silica in 100 consecutive SSc patients. Clinical characteristics and chest HRCT at diagnosis and at the latest visit were evaluated to assess the association of silica exposure with disease characteristics.

Results: 16% of the overall population and 58% of men had an occupation with specific high silica exposure. A higher silica exposure score was associated with the combination of mediastinal and hilar LA on HRCT (OR=8.09, 95%CI=2.01-32.52, P=0.002). More than 12% of the patients had a combination of mediastinal and hilar LA on HRCT. This marker of silica exposure was predictive of worsening of pulmonary involvement in univariate analysis (OR=5.86, 95%CI=1.64-20.89, P=0.007) and multivariate analysis (OR=4.57, 95%CI=1.12-18.60, P=0.034).

Conclusions: In patients with SSc, the combination of mediastinal and hilar LA on HRCT was associated with exposure to silica and was also significantly associated with a more severe evolution of ILD.

Key words: Dust exposure, Erasmus syndrome, systemic sclerosis, silica, interstitial lung disease

1. INTRODUCTION :

Systemic sclerosis (SSc) is an autoimmune disorder characterized by endothelial dysfunction, and progressive fibrosis of skin and internal organs [1]. SSc encompasses various phenotypes with high patient-to-patient variability according to clinical manifestations, autoantibody profiles, and prognosis [2]. With a prevalence ranging from 20 to 80% on high-resolution computed tomography (HRCT), pulmonary involvement is a frequent complication and remains the main cause of SSc-related death [3,4]. The most common pulmonary manifestation is SSc-related interstitial lung disease (SSc-ILD) [5]. Chest HRCT is currently the gold standard for the detection of SSc-ILD, allowing a precise assessment of the extent of the parenchymal involvement and a specific description of ILD patterns [6,7]. It has been recently demonstrated that mediastinal lymphadenopathy (LA) is a strong predictor of clinical outcomes in all-cause interstitial lung diseases, the prognostic value of mediastinal LA in SSc-ILD is yet to be further clarified [8-11].

Although SSc is mainly considered as an idiopathic disorder, many case-control and cohort studies have confirmed the association of silica exposure with SSc [12-16]. Thereby, occupational silica exposure may increase the risk of SSc with odds ratio (OR) ranging from 0.87 to 37 [12-19]. Previous studies have explored the prevalence of silica exposure in SSc, showing a high variability ranging from 1% to 15% [18, 19]. The prevalence of silica exposure in men with SSc could even reach 50% [12, 19]. A recent study has also demonstrated that silica levels were higher in the serum of patients with SSc than in healthy controls [20]. Nonetheless, the co-occurrence of silica exposure and SSc is still largely considered as a rare entity [21-23] and occupational exposures to crystalline silica seem to be frequently under-estimated. A more complete assessment of environmental exposures, using innovative and multi-faceted exposomic approaches is therefore needed in SSc [24, 25]. The recent use of new materials such as artificial stone with high silica content has been associated with a unprecedented outbreak of connective tissue diseases, including SSc [26-29]. Silica hazards are therefore still a very topical but neglected issue, even in high-income countries [30], and a specific and updated description of HRCT signs of silica exposure may help to better elucidate the importance of silica hazards in SSc patients. There are recent calls for considering LA as a marker of silica exposure, even in the absence of typical parenchymal micro-nodular involvement [31]. Nonetheless, in SSc, from a phenotypic and prognostic viewpoint, the precise relationship between chest HRCT characteristics, disease progression, and environmental inorganic dust exposure, and more specifically silica exposure, is still to be determined. Beyond parenchymal involvement, the association of lifetime silica exposure with thoracic features such as mediastinal and hilar LA on HRCT and their relationship with SSc-ILD progression is unknown.

The aim of this study was therefore to assess the association of lifetime occupational and non-occupational exposure to silica with the HRCT characteristics and the progression of pulmonary involvement in an unselected population of patients with SSc.

2. METHODS :

2.1. Patients

Between March 2016 and March 2018, patients with SSc according to ACR/EULAR 2013 classification criteria [32], followed in the department of Internal Medicine and Clinical Immunology (Rennes, France), were consecutively included in this prospective cohort study. Clinical data, pulmonary function tests and serological evaluations were performed in accordance with standard recommended practice. The study was approved by national and local ethics committees (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé – France – decision n°12.263 bis, Commission Nationale de l'Informatique et des Libertés – France – decision DR-2012-525 and decision 1980161v0). All patients gave their informed consent prior to investigations.

The disease characteristics were clinically evaluated and a silica dust exposure questionnaire was completed by patients concurrently. Patients were classified as sine scleroderma, and limited/diffuse cutaneous subsets according to LeRoy's classification [33]. Pulmonary function tests (PFTs) including total lung capacity (TLC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), were recorded at diagnosis and at the time when the exposure questionnaire was completed. According to American Thoracic Society / European Respiratory Society guidelines [34], FVC was obtained by spirometry and DLCO was measured by single-breath nitrogen test [35,36]. FVC, TLC and DLCO were expressed as % of predicted value according to the European reference equations [37,38].

2.2. HRCT evaluations

HRCT examination closest to SSc diagnosis and HRCT examination closest to questionnaire were independently evaluated by two investigators. In case of discrepancy, a new reading session was performed by a third experienced chest radiologist who made the final decision. Radiologists performing HRCT evaluation were blinded from the results of clinical and exposure evaluations.

HRCT images were evaluated at six levels : 1) the aortic arch, 2) 1cm below the level of the carina, 3) the right pulmonary venous confluence, 4) the midpoint between 3 and 5, 5) 1cm above the dome of the right hemidiaphragm and 6) 2cm below the dome of the right hemidiaphragm [39, 40]. The sixth level ensured that the posterior costophrenic recesses were evaluated [40]. SSc-ILD was defined as ground-glass opacities and reticular abnormalities, predominantly in lower lobes and subpleural area. The total extent of ILD was estimated to the nearest five percent in each of the six sections, with global extent of disease on HRCT computed as the mean of the scores. The presence of thoracic LA was evaluated. LA larger than 10 mm of the small axis, with or without calcifications were noticed. The specific combination of mediastinal and hilar LA was particularly evaluated.

The severity markers of pulmonary involvement were:

- Extensive SSc-ILD according to Goh defined as SSc-ILD extent clearly above 20% at five levels or FVC at diagnosis under 70% in indeterminate cases [41].
- Worsening of pulmonary involvement defined as an increase of pathological parenchyma extent above 10% on HRCT at questionnaire in comparison with HRCT at diagnosis, or a decrease of

FVC above 10% or DLCO above 15% of initial value at diagnosis. Patients with no CT-scan at questionnaire were considered as stable if FVC and DLCO did not decrease more than 10% and 15% of initial value at diagnosis, respectively [42].

2.3. Assessment of silica exposure

A specific questionnaire created by a multidisciplinary team of social scientists, epidemiologist, occupational health and medicine collaborators was used to assess lifetime occupational and non-occupational exposure to silica (Silicosis Questionnaire: <https://www.sciencespo.fr/silicosis/en.html>). This questionnaire thoroughly questions exposure to crystalline silica and also explores co-exposures to some other inorganic particles which frequently co-occur in situations of exposure to silica (e.g. metallic or wood particles, asbestos). This questionnaire is based on the precise factual questioning of activities and not only formal descriptions of workstations and jobs. For 45 minutes, 90 closed-ended questions relative to occupational exposures and 47 questions relative to non-occupational exposures were conducted by phone call or in a face-to-face interview by 3 trained evaluators, blinded for the results of clinical and pulmonary investigations. Samples of the questionnaire are provided in supplementary data (Supplementary Figure S1 and S2) to illustrate the type of questions and the assessment of exposure. The entire questionnaire is available on request to the corresponding author and the authorization of the authors is needed for its use for daily practice or for clinical research.

Global, occupational and non-occupational silica exposure scores were calculated for each patient. An exposure score from 0 to 5 points was calculated for each of the 90 questions taking into account the duration of exposure (less than 1 year = 1 point; between 1 and 5 years = 2 points; more than 5 years = 3 points) and the level of protection (always = 0 point; sometimes = 1 point; never = 2 points) (Supplementary Figure S3). The occupational score was expressed as the sum of all occupational exposure scores; the non-occupational score was expressed as the sum of all non-occupational exposure scores; and the global score was expressed as the sum of the occupational and non-occupational scores. The value of each score (global/occupational/non-occupational) was interpreted as a quantitative parameter but also as a qualitative parameter with a threshold value defined as higher than the second tercile of the studied population.

In order to ensure the relevance of the chosen threshold values (above the second tercile) for the quantitative exposure score and to fully explore the occupational dimension of silica hazards, we also considered occupations particularly associated with very high silica exposure as a qualitative parameter (ever have such occupation *versus* never, regardless of the score values). These occupations considered as highly exposed to silica inhalation were [43]: construction-related occupations, masons, miners, quarrymen, smelters, workers/craftsmen in the concrete industry, sandblasters, workers in tunnelling, stone carving and cutting, roofing work, tile-laying and cutting, workers in sand foundry, ceramic and glass manufacturers and dental technicians.

2.4. Statistical analysis

Qualitative data associations were analyzed conducting Chi-square test or Fisher's exact test and expressed with OR and 95% CIs. Quantitative data were analyzed conducting the unpaired two-tailed Student's t-test or Mann-Whitney U test depending on Gaussian distribution.

To ensure the independence of parameters associated with worsening of pulmonary involvement, we conducted a binary logistic regression. Clinical non-colinear parameters associated with worsening of pulmonary involvement in univariate analysis with a p -value <0.1 and with clinical relevance were included in the multivariate analysis [44]. As we expected silica exposure to be more prevalent in male, a specific stratification on gender was also performed to confirm the relevance of our findings in men only. We performed all tests with a significance level of $p<0.05$. Statistical analysis was performed using SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3.RESULTS

3.1. Clinical, HRCT and exposure characteristics

Clinical characteristics, pulmonary involvement and Silica exposures scores of the 100 patients with SSc are summarized in Supplementary Table S1. Chest HRCT at diagnosis was available for 97 patients. The mean duration between the HRCT at diagnosis and at the questionnaire was 2.92 years (SD=2.70). Thirty-five percent of patients had thoracic LA and 12% the combination of mediastinal and hilar LA at diagnosis (Figure 1). No patient had isolated hilar LA. One-third of the patients had SSc-ILD ($n=31$). Fifty-eight percent of men with SSc ($n=15$) had an occupation with high exposure to silica as previously defined.

3.2. Association of silica exposure scores with clinical and HRCT characteristics

A higher global exposure score was significantly associated with male gender, esophageal involvement and the combination of mediastinal and hilar LA (Table 1). The strongest associations were with male gender (OR=11.63, 95%CI=(4.10-33.03)) and the combination of mediastinal and hilar LA (OR=8.09, 95%CI=(2.01-32.52)). SSc-ILD at diagnosis was not associated with higher global silica exposure score *per se*. There was no association of higher non-occupational exposure score with pulmonary involvement at diagnosis (Supplementary Table S2 and S3). Smoking history was not associated with higher exposure scores.

Global and occupational silica exposure scores were significantly higher in patients with the combination of mediastinal and hilar LA in comparison with those without LA or with only isolated mediastinal LA (Table 2). Positivity of ATA, pathological parenchyma and SSc-ILD were also associated with the combination of mediastinal and hilar LA (Table 2).

To fully explore the occupational aspect of silica hazards and to ensure the relevance of the chosen threshold values (above the second tercile) for the quantitative exposure score, we also considered occupations specifically associated with intense silica exposures as a qualitative parameter (ever have such occupation *versus* never, regardless of the score values). Male gender, dcSSc, positivity for ATA, combination of mediastinal and hilar LA and pneumoconiosis were significantly associated with occupations specifically associated with high silica exposures as a qualitative parameter (Supplementary Table S4).

3.3. Stratified analysis on male gender

Since Silica exposures were highly more prevalent in men (Supplementary Table 1) and considering that men have a clinical presentation of SSc that may differ from women, we conducted a specific evaluation in men only (n=26). As a qualitative parameter, specific high occupational silica exposure in men remained associated with the combination of mediastinal and hilar LA (OR=6.5, 95%CI=1.09-38.63, p=0.046). Moreover, men with a combination of mediastinal and hilar LA had significantly higher occupational silica exposure scores than men without LA or with isolated mediastinal LA (occupational exposure scores of 34.00 (15–79) in men with the combination of mediastinal and hilar LA *versus* 20.00 (3–49) for the others, p<0.05). In men also, smoking history was not associated with higher exposure scores or specific high occupational exposures to silica (data not shown).

3.4. Markers associated with the severity of pulmonary involvement

Considering PFTs, TLC (% of predicted) was significantly lower at diagnosis in patients with higher global exposure score (TLC = 96.8 (53.0 –124.3) in the most exposed patients *versus* TLC = 118.8 (68.9 –155.0) in patients with lower exposure, p=0.024). On the contrary, FVC and DLCO were similar in higher and lower exposed groups considering global, occupational and non-occupational scores (data not shown).

FVC and TLC (% of predicted) were also significantly lower at diagnosis in patients with a combination of mediastinal and hilar LA when compared to patients without (FVC = 81.6 (59 –110) *versus* 107.5 (50 –149) respectively, p=0.002, and TLC = 89.0 (62.1 – 109.2) *versus* 111.5 (53 –155) respectively, p=0.002). On the contrary, DLCO was similar in patients with and without LA (DLCO = 70.80 (28.0 – 109.7) *versus* 70.00 (17 – 126.5) respectively, p=0.443). The same results were obtained when FVC, TLC and DLCO were considered at the time of questionnaire (p<0.005, p<0.013 and p=0.363 respectively, data not shown). Smoking history was not associated with the combination of mediastinal and hilar LA (Table 2).

In univariate analysis, the worsening of pulmonary involvement was associated with the combination of mediastinal and hilar LA, and with high occupational silica exposure score (Table 3). Classical clinical characteristics associated with a worsening of pulmonary involvement were also noticed such as male gender, dcSSc, the absence of ACA. ATA also tended to be associated with a worsening of pulmonary involvement (p=0.08). In multivariable analysis, dcSSc and the combination of mediastinal and hilar LA was still independently associated with a worsening of pulmonary involvement (Table 4).

4.DISCUSSION

In this study based on a detailed dedicated questionnaire, 16% of the overall population and 58% of men had an occupation with specific high silica exposure. The combination of mediastinal and hilar LA was associated with higher silica dust exposure and more specifically in an occupational setting. This marker of silica exposure was also associated with a worsening of pulmonary involvement independently from other classical risk factors of progression [45].

Exposure to silica is the most described occupational exposure involved in SSc, although the association is still considered rare [21-23]. Our work highlights the high prevalence of occupational exposure to silica, particularly in men, in a recent cohort of SSc patients in a high-income country. The prevalence of silica exposure in our work is consistent with other studies [12, 18, 19]. A lower prevalence was observed in Rocha and colleagues' study with only 0.9% of their population [17]. Unfortunately, no details are given concerning the precise assessment methods in this study and a retrospective evaluation of some parameters may have led to such contrasting results in comparison with previous studies and ours [17]. By using a specific questionnaire, lifetime occupational and non-occupational exposure to silica was reported in our work, through a thorough and factual questioning of activities (not only formal descriptions of workstations and jobs). This allows the calculation of global, occupational and non-occupational exposure scores. In order to ensure the relevance of the chosen threshold values (above the second tercile), we also considered occupations specifically associated with intense silica exposures as a qualitative parameter (ever *versus* none, regardless of the score). The results remained consistent.

The prevalence of silica exposure was higher in men than in women. In the literature, SSc appears to be more severe in men and the prognosis of SSc is worse in men, partly due to an increased risk of cardiovascular events [46]. To take into account this confounding bias, we conducted a stratified analysis based on gender. Even considering men only, the combination of mediastinal and hilar LA remained associated with high occupational silica exposure in SSc patients. In our entire population including men and women, mediastinal and hilar LA were also associated with high specific occupational exposure to crystalline silica considered as a qualitative parameter, confirming that thoracic LA is a relevant marker of silica exposure. Tissue sample examination and particularly biopsy of LA, although invasive, would help to confirm this result. Only four cases (4%) of pneumoconiosis have been diagnosed by radiologists who were blinded from the results of silica exposure assessment in our study whereas calcified thoracic LA and association of ILD with calcified thoracic LA were reported in 10 and 7% of patients, respectively. These three parameters were significantly associated with occupational exposure to silica. This result also supports the hypothesis that a significant proportion of patients with suspected SSc-ILD may also have dust/silica-associated fibrosis [47]. This result also suggests that, from a radiological point of view, it may appear difficult to discriminate ILD secondary to SSc from silica-associated fibrosis, particularly in men and when radiologists are not properly informed about the history of silica exposure. These results highlight the importance of a systematic specific evaluation of dust exposures to allow a more accurate interpretation of chest HRCT in SSc. Although the characteristic presentation of silicosis is a nodular, fibrosing, upper-lobe predominant disease, the combination of ILD features with LA in the context of silica exposure may also suggest silica-associated fibrosis and may be discussed thoroughly in multidisciplinary sessions associating clinicians and radiologists.

We also found that the combination of mediastinal and hilar LA was associated with SSc-ILD and a more severe evolution of pulmonary involvement in SSc, both in univariate and multivariate analysis. The definition of a worsening of pulmonary involvement used in our study included a potential decline in DLCO >15% of the baseline value [42]. Due to its impact on DLCO, this can explain that PAH on RHC was associated with worsening of pulmonary involvement, which could be considered as an unexpected result. In the sensitivity analyses, when PAH was not included in the multivariate model, the combination of mediastinal and hilar LA was still independently associated with the worsening of pulmonary involvement, strengthening the relevance of this marker as a severity marker of pulmonary involvement (Supplementary

Table S5). The prevalence of thoracic LA was 35% in our study, which is concordant with a prevalence ranging from 30 to 60% according to the literature [8, 9, 12]. Considering patients fulfilling ACR/EULAR 2013 classification criteria, Rotondo *et al.* found a high prevalence of thoracic LA (62%) and an association of thoracic LA with new onset of SSc-ILD [9]. In accordance with these results, our data also suggest that the combination of mediastinal and hilar LA, confirmed as a marker of silica exposure, is associated with SSc-ILD and with worsening of pulmonary involvement. This result is also in accordance with the results of Adegunsoye *et al.* on LA in all cause-ILD [10]. Although our results need to be validated in other independent cohorts, with larger sample size, our study suggests that significant exposure to crystalline silica with subsequent LA might be a reliable predictive marker for the severity and worsening of pulmonary involvement in SSc.

From a pathogenic viewpoint it has been recently highlighted that crystalline silica could target lung macrophages, and could alter some of their pro-resolving properties such as efferocytosis, *i.e.* the phagocytosis of apoptotic bodies, a process that down-regulates inflammation and limits autoimmunity in normal conditions [48]. By altering such a key macrophagic mechanism, crystalline silica could promote lung inflammation and lead to more severe pulmonary involvement in patients with SSc. Similarly, in mouse models of systemic lupus, inhalation of crystalline silica promotes the accumulation of apoptotic bodies and induces a more severe disease with more severe renal and pulmonary involvement [49,50]. Moreover, crystalline silica specifically activates the NLRP3 inflammasome complex in macrophages [51], a complex that is also involved in the pathogenesis of fibrosis in SSc [52]. Altogether these results suggest that exploring the relationship between silica exposure and SSc may help to identify relevant pathways that could be potential therapeutic targets for patients with SSc. The issue of silica associated-progressive ILD may also be crucial as it could help to discuss practical preventive occupational measures to limit the severity of the main cause of death in SSc [53]. And, in a therapeutic perspective, it may also help to select the patients that could benefit the most from early specific treatments to limit the extension of SSc-associated pulmonary involvement.

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Figure 1: Thoracic lymphadenopathy on high-resolution computed tomography
Calcified lymphadenopathy (LA) in a male SSc patient with occupational silica exposure such as sandblasting. Thoracic LA (arrow) defined as mediastinal (A and B) and/or hilar (C and D) LA, larger than 10 mm of the small axis, with or without calcifications.

Table 1: Association of clinical and CT characteristics with higher global (occupational+non-occupational) silica exposure score (cut off value above the second tercile) in patients fulfilling ACR/EULAR 2013 classification criteria for SSc

Parameters n (%)	Available data (n1/n2/Total)	Patients with global score above T2 n1		Patients with global score under T2 n2		OR	95%CI	p-value
Clinical characteristics								
Gender (male)	33/67/100	19	(58)	7	(10)	11.63	4.10-33.03	<0.001
Age (above mean)	33/67/100	23	(70)	33	(49)	2.37	0.98-5.73	0.058
Smoking history	33/67/100	17	(52)	32	(48)	1.16	0.51-2.68	0.724
dcSSc	33/67/100	13	(39)	15	(22)	2.25	0.91-5.56	0.075
lcSSc	33/67/100	19	(58)	45	(67)	0.66	0.28-1.57	0.348
SSc sine scleroderma	33/67/100	1	(3)	7	(10)	0.27	0.03-2.27	0.265
Scleroderma Renal Crisis	33/67/100	0	(0)	1	(1)	NA	NA	1.00
Ischemic Digital Ulcers (Current or past)	33/67/100	17	(52)	25	(37)	1.79	0.77-4.15	0.201
Skin telangiectasia	33/67/100	24	(73)	47	(70)	1.13	0.45-2.87	1.00
PAH on RHC	33/67/100	1	(3)	6	(9)	0.32	0.04-2.75	0.42
Oesophageal involvement	33/67/100	21	(64)	27	(40)	2.59	1.10-6.13	0.028
FVC<70% of predicted	32/60/92	4	(13)	5	(8)	1.57	0.39-6.32	0.052
DLCO<70% of predicted	33/66/99	16	(48)	36	(54)	0.78	0.34-1.81	0.569
Immunosuppressive drugs (current or past)	33/67/100	15	(45)	16	(24)	2.66	1.10-6.44	0.039
Immunological findings								
ACA	33/67/100	16	(48)	31	(46)	1.09	0.47-2.52	1.00
ATA	33/67/100	9	(27)	15	(22)	1.30	0.50-3.39	0.62
Anti-RNA pol III	33/67/100	1	(3)	2	(3)	1.02	0.09-11.62	1.00
Anti-PmScl	33/67/100	1	(3)	2	(3)	1.01	0.089-11.62	1.00
Anti-U1 RNP	33/67/100	0	(0)	1	(1)	NA	NA	0.48
Anti-Fibrillarin	33/67/100	2	(6)	3	(4)	1.38	0.22-8.67	0.73
Anti-Th/To	33/67/100	0	(0)	2	(3)	NA	NA	0.32
Anti-Trim21 (SSA 52kD)	33/67/100	1	(3)	3	(4)	0.67	0.07-6.67	0.73
Anti-Ku	33/67/100	0	(0)	1	(1)	NA	NA	0.48
Anti-SRP	33/67/100	1	(3)	0	(0)	NA	NA	0.152
ANA positivity but without specificity	33/67/100	2	(6)	9	(13)	0.42	0.09-2.05	0.268
Pulmonary characteristics on HRCT at diagnosis								
Combination of mediastinal and hilar LA	32/65/97	9	(28)	3	(5)	8.09	2.01-32.52	0.002
Calcified LA	32/65/97	5	(16)	5	(8)	2.22	0.59-8.32	0.29
SSc-associated ILD	32/65/97	10	(31)	21	(32)	0.95	0.38-2.37	1.00
Pneumoconiosis (silicosis and/or asbestosis)	32/65/97	1	(3)	3	(5)	0.67	0.067-6.67	1.00
Severity markers of pulmonary involvement								
Extensive SSc associated ILD according to Goh	32/65/97	4	(13)	9	(14)	0.89	0.25-3.14	1.00
Worsening of pulmonary involvement#	31/64/95	10	(32)	13	(20)	1.86	0.71-4.92	0.21

SSc: Systemic sclerosis, T2: second tercile, OR: odds ratio, CI: confidence interval, dcSSc: diffuse cutaneous SSc, lcSSc: limited cutaneous SSc, PAH: pulmonary arterial hypertension, RHC: right heart catheterization, ACA: anticentromere antibodies, ATA: anti-Scl-70/topoisomerase I antibodies, anti-RNA pol III: anti-RNA polymerase III antibodies, ANA: Antinuclear antibodies, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for

carbon monoxide, HRCT: high-resolution computed tomography, LA: lymphadenopathy, ILD: interstitial lung disease.
#Worsening of pulmonary involvement: increase of pathological parenchyma extent above 10% on HRCT at questionnaire in comparison with HRCT at diagnosis, or a decrease of FVC above 10% or DLCO above 15% of initial value at diagnosis for patients with only HRCT at diagnosis.

Table 2: Association of clinical and CT-characteristics with the association of mediastinal and hilar lymphadenopathies

Parameters n (%)	Available data (n1/n2/Total)	Patients with med. and hilar LA n1		Patients without LA or with med. LA only n2		OR	95%CI	p-value
Clinical characteristics								
Gender (male)	12/85/97	10	(83)	16	(19)	21.56	4.30-108.16	<0.001
Age (above mean)	12/85/97	6	(50)	48	(56)	0.77	0.23-2.59	0.76
Smoking history	12/85/97	8	(67)	40	(47)	2.25	0.63-8.04	0.233
dcSSc	12/85/97	6	(50)	22	(26)	2.86	0.84-9.81	0.100
lcSSc	12/85/97	6	(50)	55	(64)	0.55	0.16-1.84	0.352
SSc sine scleroderma	12/85/97	0	(0)	8	(9)	NA	NA	0.590
Scleroderma Renal Crisis	12/85/97	0	(0)	1	(1)	NA	NA	1.00
Ischemic Digital Ulcers (current or past)	12/85/97	5	(42)	35	(41)	1.02	0.30-3.48	1.00
Skin telangiectasia	12/85/97	5	(42)	64	(75)	0.23	0.07-0.82	0.035
PAH on RHC	12/85/97	1	(8)	6	(7)	1.20	0.13-10.90	1.00
Oesophageal involvement	12/85/97	6	(50)	40	(47)	1.13	0.34-3.77	1.00
FVC<70% of predicted	12/77/89	5	(42)	4	(5)	13.04	2.83-59.99	0.002
DLCO<70% of predicted	11/85/96	5	(45)	47	(55)	0.67	0.19-2.38	0.75
Immunosuppressive drugs (current or past)	12/85/97	8	(67)	22	(26)	5.73	1.57-20.90	0.007
Immunological findings								
ACA	12/85/97	1	(8)	43	(51)	0.089	0.01-0.72	0.006
ATA	12/85/97	6	(50)	18	(21)	3.72	1.07-12.93	0.03
Anti-RNA pol III	12/85/97	0	(0)	3	(4)	NA	NA	1.00
Anti-PmScl	12/85/97	2	(17)	1	(1)	16.80	1.40-202.30	0.04
Anti-U1 RNP	12/85/97	0	(0)	1	(1)	NA	NA	1.00
Anti-Fibrillarin	12/85/97	0	(0)	5	(5)	NA	NA	1.00
Anti-Th/To	12/85/97	0	(0)	2	(1)	NA	NA	1.00
Anti-Trim21 (SSA 52kD)	12/85/97	0	(0)	4	(5)	NA	NA	1.00
Anti-Ku	12/85/97	0	(0)	1	(1)	NA	NA	1.00
Anti-SRP	12/85/97	1	(8)	0	(0)	NA	NA	0.12
ANA positivity but without specificity	12/85/97	2	(17)	9	(10)	1.69	0.32-8.95	0.62
Inorganic dust exposure								
Global score above T2	12/85/97	9	(28)	23	(27)	8.09	2.01-32.52	0.002
Occupational score above T2	12/85/97	9	(27)	24	(28)	7.63	1.90-30.59	0.003
Extra-occupational score above T2	12/85/97	5	(17)	25	(29)	1.71	0.50-5.92	0.51
Pulmonary characteristics on HRCT at diagnosis								
SSc-associated ILD	12/85/97	7	(58)	24	(28)	3.56	1.03-12.31	0.049
Pneumoconiosis (silicosis and/or asbestosis)	12/85/97	1	(8)	3	(4)	2.49	0.24-26.03	0.42
Severity markers of pulmonary involvement								
Extensive SSc-associated ILD according to Goh	12/85/97	4	(33)	9	(11)	4.22	1.06-16.87	0.03
Worsening of pulmonary involvement	12/83/95	7	(58)	16	(19)	5.86	1.64-20.89	0.007

SSc: Systemic sclerosis, T2 : second tercile, OR: odds ratio, CI: confidence interval, dcSSc: diffuse cutaneous SSc, lcSSc: limited cutaneous SSc, PAH: pulmonary arterial hypertension, RHC: right heart catheterization, ACA: anticentromere antibodies, ATA: anti-Scl-70/topoisomerase I antibodies, anti-RNA pol III: anti-RNA polymerase III antibodies, ANA: Antinuclear antibodies, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, HRCT: high-resolution computed tomography, LA: lymphadenopathy, ILD: interstitial lung disease.

#Worsening of pulmonary involvement: increase of pathological parenchyma extent above 10% on HRCT at questionnaire in comparison with HRCT at diagnosis, or a decrease of FVC above 10% or DLCO above 15% of initial value at diagnosis for patients with only HRCT at diagnosis.

Table 3: Clinical and CT-characteristics associated with worsening of pulmonary involvement (univariable analysis)

Parameters n (%)	Available data (n1/n2/Total)	Worsening of pulmonary involvement #		No worsening of pulmonary involvement		OR	95%CI	p-value
		n1		n2				
Clinical characteristics								
Gender (male)	23/72/95	11	(48)	14	(19)	3.80	1.39-10.37	0.007
Age (above mean)	23/72/95	12	(52)	41	(57)	0.83	0.32-2.12	0.69
Smoking history	23/72/95	15	(65)	32	(44)	2.34	0.88-6.22	0.08
dcSSc	23/72/95	11	(48)	17	(24)	2.97	1.11-7.92	0.03
lcSSc	23/72/95	11	(48)	48	(67)	0.45	0.177-1.19	0.105
SSc sine scleroderma	23/72/95	1	(4)	7	(10)	0.42	0.049-3.63	0.675
Scleroderma Renal Crisis	23/72/95	0	(0)	1	(1)	NA	NA	1.00
Ischemic Digital Ulcers (current or past)	23/72/95	15	(65)	25	(35)	3.53	1.32-9.45	0.01
Skin telangiectasia	23/72/95	19	(83)	49	(68)	2.23	0.68-7.30	0.18
PAH on RHC	23/72/95	5	(22)	1	(1)	19.72	2.17-179.50	0.003
Oesophageal involvement	23/72/95	12	(52)	34	(47)	1.22	0.48-3.12	0.68
FVC<70% of predicted	20/67/87	6	(30)	3	(4)	9.14	2.04-41.04	0.004
DLCO<70% of predicted	22/72/94	15	(68)	35	(49)	2.27	0.83-6.22	0.11
Immunosuppressive drugs (current or past)	23/72/95	13	(57)	17	(24)	4.21	1.57-11.29	0.003
Immunological findings								
ACA	23/72/95	4	(17)	38	(53)	0.19	0.06-0.61	0.003
ATA	23/72/95	9	(39)	15	(21)	2.44	0.89-6.72	0.08
Anti-RNA pol III	23/72/95	1	(4)	2	(3)	1.59	0.14-18.40	0.71
Anti-PmScl	23/72/95	2	(9)	1	(1)	6.76	0.58-78.31	0.14
Anti-U1 RNP	23/72/95	1	(4)	0	(0)	NA	NA	0.24
Anti-Fibrillarin	23/72/95	1	(4)	4	(6)	0.77	0.08-7.28	1.00
Anti-Th/To	23/72/95	0	(0)	2	(3)	NA	NA	1.00
Anti-Trim21 (SSA 52kD)	23/72/95	1	(4)	3	(4)	1.04	0.10-10.57	1.00
Anti-Ku	23/72/95	0	(0)	1	(1)	NA	NA	1.00
Anti-SRP	23/72/95	1	(4)	0	(0)	NA	NA	0.24
ANA and no specificity	23/72/95	3	(13)	8	(11)	1.20	0.29-4.96	0.72
Pulmonary characteristics on HRCT at diagnosis								
Combination of mediastinal and hilar LA	23/72/95	7	(30)	5	(7)	5.86	1.64-20.89	0.007
Calcified mediastinal LA	23/72/95	6	(26)	4	(6)	6.00	1.52-23.66	0.012
SSc-associated ILD	23/72/95	14	(61)	17	(24)	5.03	1.85-13.66	0.001
Pneumoconiosis (silicosis and/or asbestosis)	23/72/95	2	(9)	2	(3)	3.33	0.44-25.12	0.25
Inorganic dust exposure								
Global score above T2	23/72/95	10	(43)	21	(29)	1.87	0.71-4.92	0.20
Occupational score above T2	23/72/95	12	(52)	21	(29)	2.65	1.01-6.94	0.044
Extra-occupational score above T2	23/72/95	6	(26)	22	(31)	0.80	0.28-2.31	0.68

SSc: Systemic sclerosis, T2: second tercile, OR: odds ratio, CI: confidence interval, dcSSc: diffuse cutaneous SSc, lcSSc: limited cutaneous SSc, PAH: pulmonary arterial hypertension, RHC: right heart catheterization, ACA: anticentromere antibodies, ATA: anti-Scl-70/topoisomerase I antibodies, anti-RNA pol III: anti-RNA polymerase III antibodies, ANA: Antinuclear antibodies, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, HRCT: high-resolution computed tomography, LA: lymphadenopathy, ILD: interstitial lung disease.

Worsening of pulmonary involvement: increase of pathological parenchyma extent above 10% on HRCT at questionnaire in comparison with HRCT at diagnosis, or a decrease of FVC above 10% or DLCO above 15% of initial value at diagnosis for patients with only HRCT at diagnosis.

Table 4: Clinical and CT-characteristics associated with worsening of pulmonary involvement (multivariate analysis) in patients with SSc

Parameters n (%)	OR	95%CI	p-value
Gender (male)	-	-	0.40
Smoking history	3.12	0.93-10.43	0.065
dcSSc	3.65	1.14-11.67	0.029
PAH on RHC	46.68	4.04-538.80	0.002
ATA	-	-	0.39
Combination of mediastinal and hilar LA	4.57	1.12-18.60	0.034

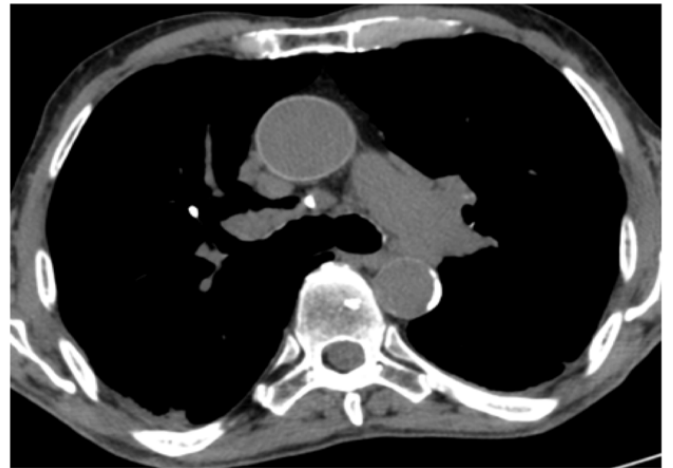
SSc: Systemic sclerosis, OR: odds ratio, CI: confidence interval, dcSSc: diffuse cutaneous SSc, PAH: pulmonary arterial hypertension, RHC: right heart catheterization, ATA: anti-Scl-70/topoisomerase I antibodies, LA: lymphadenopathy.

#Worsening of pulmonary involvement: increase of pathological parenchyma extent above 10% on HRCT at questionnaire in comparison with HRCT at diagnosis, or a decrease of FVC above 10% or a decrease of DLCO above 15% of initial values at diagnosis for patients with only HRCT at diagnosis.

A



B



C



D

