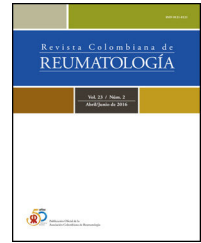




Asociación
Colombiana de
Reumatología®

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma



Review article

Systemic sclerosis and interstitial lung disease: From pathogenesis, to screening, diagnosis, and classification

Helena Codes^a, Aslihan Avanoglu Guler^{b,c}, Corrado Campochiaro^c,
Marco Matucci Cerinic^c, Ivan Castellvi^{a,*}

^a Department of Rheumatology, Hospital Universitari de la Santa Creu i Sant Pau, Barcelona, Spain

^b Department of Internal Medicine, Division of Rheumatology, Gazi University Hospital, Ankara, Turkey

^c Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy

ARTICLE INFO

Article history:

Received 29 May 2023

Accepted 11 July 2023

Available online 17 October 2023

Keywords:

Systemic sclerosis

Interstitial lung disease

Lung

Treatment

Approach

ABSTRACT

Interstitial lung disease (ILD) is a common and potentially devastating complication of systemic sclerosis (SSc), a chronic autoimmune disorder characterized by fibrosis and vascular abnormalities. The association between SSc and ILD underscores the intricate interplay between immune dysregulation, vasculopathy, and tissue fibrosis. This review provides a comprehensive overview of the immunological, clinical, and radiological features of ILD in the context of SSc. It highlights the diverse spectrum of ILD patterns observed in SSc patients, ranging from non-specific interstitial pneumonia to usual interstitial pneumonia. The intricate pathogenic mechanisms linking SSc and ILD involve aberrant immune responses, endothelial dysfunction, profibrotic cytokine signaling, and genetic factors. Immunological alterations, diagnostic challenges, and prognostic implications are discussed, underscoring the need for multidisciplinary management strategies. By elucidating the complex relationship between SSc and ILD, this review aims to contribute to a deeper understanding of the underlying mechanisms and facilitate the development of interdisciplinary interventions for improved patient outcomes.

© 2023 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

* Corresponding author.

E-mail address: Castellvi@santpau.cat (I. Castellvi).

<https://doi.org/10.1016/j.rcreu.2023.09.001>

0121-8123/© 2023 Asociación Colombiana de Reumatología. Published by Elsevier España, S.L.U. All rights reserved.

Esclerosis sistémica y enfermedad pulmonar intersticial: de la patogenia al cribado, el diagnóstico y la clasificación

R E S U M E N

Palabras clave:

Esclerosis sistémica
Enfermedad intersticial
pulmonar
Pulmón
Tratamiento
Abordaje

La enfermedad pulmonar intersticial (EPI) es una complicación frecuente y potencialmente devastadora de la esclerosis sistémica (SSc), un trastorno autoinmune crónico caracterizado por fibrosis y anomalías vasculares. La asociación entre la SSc y la EPI subraya la difícil interacción entre la desregulación inmunitaria, la vasculopatía y la fibrosis tisular. Esta revisión proporciona una visión global de las características inmunológicas, clínicas y radiológicas de la EPI en el contexto de la SSc; de igual manera, se destaca el diverso espectro de patrones de EPI observados en pacientes con SSc, que van desde la neumonía intersticial inespecífica a la habitual. Los intrincados mecanismos patogénicos que relacionan la SSc y la EPI implican respuestas inmunitarias aberrantes, disfunción endotelial, señalización profibrótica de citoquinas y factores genéticos. Se discuten las alteraciones inmunológicas, los retos diagnósticos y las repercusiones pronósticas, subrayando la necesidad de estrategias de gestión multidisciplinarias. Al elucidar la compleja relación entre la SSc y la EPI, esta revisión pretende contribuir a una comprensión más profunda de los mecanismos subyacentes y facilitar el desarrollo de intervenciones interdisciplinarias para mejorar los resultados de los pacientes.

© 2023 Asociación Colombiana de Reumatología. Publicado por Elsevier España, S.L.U.
Todos los derechos reservados.

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder which can progress with multiple life-threatening organ involvement including interstitial lung disease (ILD). To date, three pathogenic pathways for the development of SSc have been implicated, including immune dysregulation, vasculopathy, and progressive fibrosis. ILD is one of the most common manifestations of SSc and a primary contributor to SSc-related deaths, followed by pulmonary arterial hypertension and cardiac causes.¹⁻³ The clinical presentations of SSc-related ILD (SSc-ILD) vary from asymptomatic with stable lung function to severe dyspnea and cough with progressive lung involvement.⁴ Considering the complex nature and heterogenous clinical presentation of SSc-ILD, both proper assessment of patients for early diagnosis and management and better understanding of the disease pathogenesis are crucial for mitigating the detrimental consequences of SSc-ILD and development of better, and someday, curative treatments.

The pathogenesis of SSc-related ILD

Results of clinical and preclinical animal-based studies have revealed that SSc-ILD proceeds from various complex pathways which might be summarized in endothelial and epithelial lung injury. There is dysregulation of the immune system including innate and adaptive immune cells with an increase in pro-inflammatory and pro-fibrotic cytokines, eventually resulting in fibrosis with exaggerated deposition of extracellular matrix (ECM).⁵ However, there are still major areas of uncertainty regarding the pathogenesis of SSc-ILD.

The role of lung/tissue injury in SSc-ILD

Repetitive and sustained injury of alveolar endothelial and epithelial cells is believed to be the initial step for the development of ILD-SSc.^{6,7} Thrombin, a procoagulant factor, is released after tissue and vascular injury. Bronchoalveolar fluid (BAL) from patients with SSc who have pulmonary fibrosis demonstrates a remarkable increase in thrombin activity with associated mitogenic activity of thrombin on lung fibroblasts that may be related to pulmonary fibrosis.⁸ As well, thrombin promotes the differentiation of lung fibroblasts into myofibroblasts, which is the cornerstone of the fibrotic process.⁹ The preclinical studies assessing the inhibition of thrombin have demonstrated that dabigatran, a direct thrombin inhibitor, reduces the myofibroblast differentiation of lung fibroblasts and pulmonary fibrosis.^{10,11} However, at the clinical level, a study evaluating the tolerability and safety of dabigatran in patients with SSc-ILD failed to show an effect of dabigatran on pulmonary function tests (PFTs).¹²

Another possible mediator released after lung injury is endothelin-1 (ET-1) which is a strong vasoconstrictor and is secreted by endothelial cells, epithelial cells, and alveolar macrophages. ET-1 has pro-inflammatory and pro-fibrotic effects by activating the neutrophil aggregations, cytokine production and inducing fibroblasts, and promoting endothelial-mesenchymal transition (EndoMT).¹³⁻¹⁵ The pathologic assessment of lung tissue from patients with SSc-ILD has revealed a marked increase in expression of ET-1 and its receptors.¹⁶ Furthermore, serum ET-1 level has been found to be significantly increased in serum and BAL from patients with SSc-ILD in previous studies.¹⁷⁻¹⁹ Moreover, the evaluation of patients with SSc with nailfold video capillaroscopy has elu-

citated that peripheral microvascular abnormalities reflecting the endothelial damage are related to ILD, supporting the role of microvascular injury in the pathogenesis of SSc-ILD.²⁰

Alveolar epithelial cells (AECs) divide into two cell subsets. Type I AECs comprise the majority of the alveolar epithelial line, and type II AECs, which are proliferating cells with a high regeneration capacity and are responsible for production of surfactants.^{21,22} Apart from surfactants, type II AECs produce a mucin-like glycoprotein, called Krebs von den Lungen-6 (KL-6). The level of KL-6 increases with alveolar epithelial damage or cellular regeneration.²³ KL-6 induces lung fibroblast proliferation while inhibiting the apoptosis of fibroblasts.²⁴ The serum level of KL-6 is found to be markedly elevated in SSc-ILD and related to the severity of lung involvement.^{25,26} After epithelial alveolar injury, type II AECs start to proliferate and some undergo apoptosis while the remaining cells differentiate into type I AECs in normal repair. However, in pathologic conditions such as idiopathic pulmonary fibrosis or SSc-ILD, type II AECs have been implicated in fibrosis due to their capacity for endothelial-mesenchymal transition (EMT) through transforming-growth factor beta (TGF- β) signaling.^{22,27} Furthermore, alveolar macrophages and type II AECs are considered as a TGF- β secreting cells in SSc with fibrosing alveolitis.²⁸ Similar to AECs, lung endothelial cells can differentiate into fibroblasts in bleomycin-induced lung injury and fibrosis.²⁹ The immunohistopathological investigation of lung tissue has demonstrated the occurrence of EndoMT in SSc-ILD.³⁰

The role of inflammation and alteration of immune cells in SSc-ILD

Alveolitis-inflammation

Alveolitis, the infiltration of alveoli with inflammatory and immune cells, is reflected in an increased percentage of neutrophils, lymphocytes or eosinophils in BAL.³¹ The results of numerous studies revealed a prominent granulocytosis (neutrophilia and eosinophilia) in BAL from patients with SSc-ILD.³² Moreover, significant neutrophilia on BAL is found in patients with SSc even with normal findings on computed tomography (CT) of the chest compared to healthy participants.³³ Histopathologic examination of the lung in patients with SSc at an early stage has shown interalveolar inflammation with a higher number of macrophages and infiltration of the interstitium with lymphocytes and plasma cells. As well, inflammation and fibrosis are found together which may support the role of inflammation in the fibrosis of SSc-ILD. Interestingly, occasional polymorphonuclear cells in alveolar space are detected in contrast to BAL findings.³⁴ In BAL or sera of patients with SSc-ILD, the levels of pro-inflammatory markers such as interleukin (IL)-6, IL-8, IL-4, monocyte chemoattractant protein-1 (MCP-1), leukotriene B₄, and leukotriene E₄ are increased.³⁵⁻³⁹ All these results strongly suggest that inflammation may play a pivotal role in the pathogenesis of SSc-ILD.

T cells

Activated specific adaptive immune cells including T helper (Th)2 cells, Th22 cells, Th17 cells, and B cells participate in the pathogenesis of SSc-ILD.²² The differentiation toward

Th2 cells, which have a profibrotic phenotype, has been observed in SSc. IL-4 and IL-13, mainly produced by Th2 cells, have profibrotic effects through the activation of fibroblast and promoting collagen synthesis via the TGF- β pathway.⁴⁰ Another important role of these cytokines is the activation of macrophages with the profibrotic phenotype (M2 polarization) which has been suggested to play a role in the fibrotic process in SSc.⁴¹ The level of IL-4 is significantly higher in BAL and sera of patients with SSc-ILD.^{36,39} A recent study has demonstrated a significant association between IL-13 level and severity of ILD in SSc.⁴² Moreover, the frequency of CD4⁺ T cells producing IL-22 is shown to be elevated in patients with SSc-ILD, and the level of serum IL-22 is positively correlated with the presence of ILD in SSc.^{43,44}

Several studies have evaluated the role of regulatory T (Treg) cells in SSc. These cells are responsible for maintaining immune homeostasis and suppressing effector immune cells. Several studies have demonstrated a remarkable decline in circulating Treg cells in SSc, although a few studies have shown a significant increase in Treg cells.⁴⁵ A study with a small number of patients with SSc reported a significant increase in the ratio of Treg cells and Th17 cells in SSc compared to healthy controls.⁴⁶ This study also reported an elevated percentage of Treg cells in patients with high ILD scores on CT and in patients with decreased carbon monoxide diffusing capacity (DLCO).⁴⁶ Another recent study reported that patients with SSc-ILD have a higher number of Treg cells than healthy controls.⁴⁷ Moreover, the level of IL-35, secreted mainly by Treg cells, is found to be increased in patients with SSc who have 94% of the lung involved. The level of IL-35 is positively associated with Treg cells and high-resolution computerized tomography (HRCT) PFT lung scores.⁴⁸ These results might be explained by the diminished suppressive effect of Treg cells in SSc.^{49,50}

IL-33 is released from stromal cells such as epithelial cells, endothelial cells, and fibroblasts after tissue injury or cell damage.⁵¹ IL-33 promotes polarization of M2 macrophages and differentiation of Treg cells into Th2 cells and thus attenuates dermal and pulmonary fibrosis through IL-13-dependent fibrotic pathways.^{51,52} The serum level of IL-33 is significantly increased in patients with SSc, especially those with microvascular involvement and skin and pulmonary fibrosis, and is correlated with the severity of pulmonary and skin fibrosis.^{53,54}

B cells

The dysregulation of B cell immunity including hyperactivation of B cells with production of autoantibodies, alteration of B cell homeostasis, and imbalance between B cell subsets, plays a fundamental role in the pathogenesis of SSc.⁵⁵ The investigation of lung tissue samples from patients with SSc-ILD has indicated that there are prominent B cell infiltrations in most of the lung specimens in addition to T cell infiltrations.⁵⁶

B regulatory (Breg) cells secrete IL-10, which has potent anti-inflammatory and anti-fibrotic effects, and inhibit CD4⁺ T cell proliferation and differentiation of Th1 and Th17 cells.⁵⁷ Recent reports have revealed that patients with SSc-ILD have a markedly decreased count of Breg cells compared to patients with SSc but without ILD.^{58,59} Effector B (Beff) cells or activated B cells are responsible for the production of autoantibodies,

inducing collagen synthesis of fibroblasts and promoting fibrosis through secretion of IL-6 and TGF- β .⁵⁵ A significantly higher level of IL-6-producing Beff cells and decreased level of IL-10-producing Breg cells is observed in patients with SSc compared to healthy controls. There is also a positive correlation between effector B (Beff)/Breg cells ratio and extent of ILD in SSc.⁶⁰ In patients with SSc-ILD, a significant increase in serum IL-6 level is detected compared to patients with SSc without ILD, and the level of IL-6 is predictive for deterioration of lung function tests.^{61,62} Another important effect of B cells on SSc is to produce disease-specific autoantibodies such as anti-topoisomerase I autoantibody (ATA) and anti-centromere autoantibody believed to be a contributor to SSc pathogenesis.⁶³ ATA positivity is a strong predictor for the development of ILD in SSc.⁶⁴

Fibroblasts–myofibroblasts

Myofibroblasts and fibroblasts are the main driving cells leading to fibrosis through excessive ECM deposition in ILD. Myofibroblasts are derived from various cell types including fibroblasts activated by profibrotic mediators and stimuli, circulating fibrocytes, and mesenchymal transition of epithelial and endothelial cells (EMT and EndoMT).⁴¹ In SSc, cultured fibroblasts derived from BAL have overexpression of myofibroblast phenotype markers such as alpha-smooth muscle cell actin (α -SMA), vimentin, and desmin with increased collagen production.⁶⁵

Screening

Given the devastating consequences of SSc-ILD including its higher mortality rate and negative effects on quality of life, the screening for ILD in SSc has become crucial to early diagnosis and appropriate management.^{1,66} Notwithstanding this imperative, there are still no formal, universally acknowledged screening guidelines for SSc-ILD. Patients with SSc who should be considered for ILD screening are especially those with risk factors for the development of ILD. These risk factors are considered to be dcSSc, presence of anti-topoisomerase I antibody, male sex, African American ethnicity, presence of respiratory symptoms, and history of smoking.⁶⁷ Screening for ILD in SSc usually involves careful evaluation of pulmonary symptoms, physical examination, PFTs, and HRCT. All patients with SSc should be examined with lung auscultation, especially for velcro-like crackles, and also respiratory symptoms such as cough and dyspnea should be reviewed to assess the lung involvement at every visit. However, a Canadian research group has shown that the diagnosis of ILD based upon physical examination (presence of basilar velcro-like crackles) and/or chest imaging with radiography has lower sensitivity compared to forced vital capacity (FVC) % predicted in patients with SSc, but higher specificity.

According to expert consensus, PFTs should be ordered in all patients with SSc and repeated regularly.⁶⁷ Screening PFTs are usually performed and repeated within six to twelve months. The most commonly assessed PFT parameters are FVC and diffusion capacity of carbon monoxide (DLCO). However, some patients with SSc, particularly those with anti-

topoisomerase antibodies, have normal FVC and DLCO values despite the presence of fibrosis on HRCT.⁶⁸

Results of several studies have revealed that these PFT parameters have low sensitivity and specificity for diagnosing ILD in patients with SSc.^{68,69} PFTs also have poor sensitivity for detecting ILD in patients with early diffuse cutaneous systemic sclerosis (dcSSc).⁷⁰ However, an EUSTAR report on a very large number of patients has shown that DLCO is the earliest functional parameter to be reduced in SSc-ILD⁷¹ and that it correlated very well with HRCT changes.⁷² Taken together, this evidence suggests that the PFTs may raise the suspicion of an ongoing interstitial process but are not sufficient to diagnose ILD in patients with SSc.

HRCT is considered as the gold standard tool for the detection of ILD in SSc.^{73,74} HRCT provides valuable findings including the pattern of ILD and the severity or extent of fibrosis, findings that correlate with disease prognosis.⁷⁵ The reports of a survey evaluating the approach of rheumatologists for screening SSc-ILD have revealed that HRCT is used in newly diagnosed patients with SSc by 66% of SSc experts and 51% of general rheumatologists.⁷³ Another survey analysis has shown that 65% of responders routinely use HRCT as a screening tool for ILD in patients newly diagnosed SSc, and 30.7% of responders perform HRCT when clinical indicators of ILD such as a decline in PFTs (FVC < 80% predicted), crackles on auscultation or dyspnea are present.⁷⁶ A recent prospective study has reported that the majority of patients with SSc undergo HRCT.⁷⁷ Use of HRCT is related to the presence of anti-centromere autoantibody and missing FVC values in patients followed at SSc-expert centers.⁷⁷

Expert consensus guidelines recommend that HRCT should be performed in all patients with SSc to screen for ILD.^{67,78} However, there is no consistency in the recommended screening interval with HRCT. Generally, the frequency of obtaining HRCT should be based on the clinician's decision taking into account risk factors for the development of ILD.⁶⁷

Recent evidence has suggested that lung ultrasound may be a promising imaging tool for ILD screening because of its high sensitivity to detect parenchymal modifications in SSc.⁷⁹⁻⁸¹ The results of an assessment of ILD in SSc with lung ultrasound have shown an inverse relationship between B-lines and pulmonary function tests and a significant correlation between B-lines and HRCT scores. While currently not widely studied or used for ILD screening, lung ultrasound may emerge as a possible modality for identifying ILD in SSc.⁸²

ILD diagnosis in SSc

The clinical course of systemic sclerosis (SSc) is variable. ILD in SSc may be asymptomatic, or present as exertional dyspnea or persistent dry cough.⁸³ However, dyspnea in SSc may be multifactorial and caused also by vascular disease, musculoskeletal involvement, anemia or cardiac disease.⁸⁴

Pulmonary complications are the leading cause of disease-related mortality in SSc.⁸⁵ ILD was the leading cause of death in a EUSTAR reported cohort of over 5800 patients; 35% of all SSc-related deaths were related to pulmonary fibrosis.⁸⁶

ILD is present in up to 80% of patients with SSc⁸⁷ and frequently appears during the first 4–6 years after the disease onset. It is noteworthy that most patients with ILD will develop

severe restrictive lung disease in the first 5 years after the onset of symptoms.⁸⁸ PFT are neither sensitive nor specific enough to detect early ILD. HRCT is the standard test for confirming the diagnosis.⁸⁹⁻⁹¹ Histological study of the lung is not considered as a routine tool to diagnosis ILD in SSc and is reserved for cases of diagnostic uncertainty.^{92,93}

Lung parenchyma involvement in SSc can be due to causes other than ILD and. Patients with SSc-ILD may also have other forms of lung disease as well. Immunosuppressive treatment predisposes to lung infections including COVID19. Carcinoma and pulmonary lymphangitic carcinomatosis can simulate ILD, so that neoplastic processes must be considered in the differential diagnosis of ILD. Other conditions that should be considered in the differential diagnosis of ILD are exposure-related lung disease such as asbestosis, and chronic hypersensitivity pneumonitis.⁹⁴

Primary heart involvement or arrhythmia due to SSc can cause left heart dysfunction (LDH) and can also mimic symptoms of ILD. Pulmonary veno-occlusive disease (PVOD) shares some radiological findings with ILD. Transthoracic echocardiography is a useful tool to screen for pulmonary arterial hypertension (PAH) and can help in cases where PAH or left heart disease is suspected.⁹⁵

Other pulmonary complications of SSc include the underlying connective tissue disease of the chest wall skin that may directly restrict respiratory movement, and muscle involvement with inflammation or fibrosis that impairs ventilation of the lungs.^{84,85} Pleural disease can occur with pleural effusions, although it is less common than in other CTDs (connective tissue diseases) and may be a clinical indication of an overlap syndrome.

Finally, it is always important to exclude, even if uncommon, the possibility of iatrogenesis caused by immunosuppressive therapy such as acute methotrexate toxicity⁹⁶ or amiodarone toxicity.⁹⁷

ILD classification in SSc

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) can be classified by different ways. It can be categorized by lung-tissue histology, high-resolution computerized tomography (HRCT) imaging-pattern, radiographic extent of disease and likelihood of progression.

The main histological features of SSc-ILD are based on parenchymal infiltration of inflammatory cells and subsequent fibrosis of the lung tissue.^{98,99} The cellular composition of the infiltrates and the disorganization and dysregulation of the lung parenchyma define the different patterns that can be identified. Due to usually good radiologic-histologic pattern correlation, lung biopsy is not usually required.⁹³ HRCT is usually sufficient confirming ILD and characterizing the type of interstitial changes with a high degree of reliability. Lung biopsy is usually done in cases where malignancy, infection, or other conditions such as hypersensitivity pneumonitis are suspected.

The histological ILD subsets seen in SSc-ILD include non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP) and lymphoid interstitial pneumonia (LIP). In SSc-ILD, NSIP is the most com-

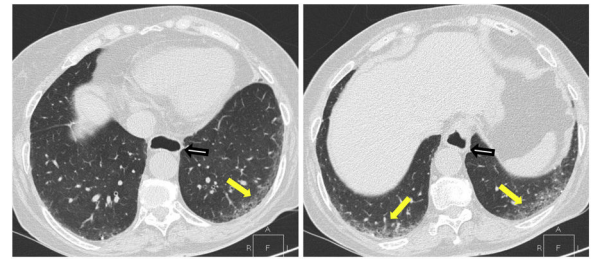


Fig. 1 – (A, B) High resolution computed tomography demonstrating NSIP with subpleural ground-glass opacities (short arrows) with traction bronchiectasis (arrows) and sparing of the subpleural lung.

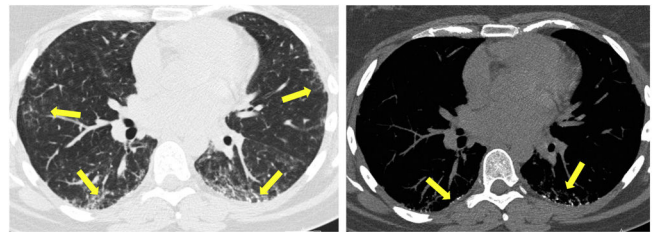


Fig. 2 – (A) NSIP with subpleural multifocal patchy ground-glass opacities (arrows); (B) subpleural dendriform ossification is also observed (arrows).

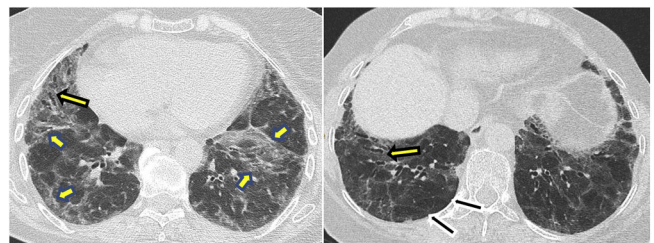


Fig. 3 – (A, B) Fibrotic NSIP with subpleural sparing. HRCT shows multifocal patchy ground-glass opacities (short arrows) with traction bronchiectasis (arrows) and sparing of the subpleural lung (black arrows).

mon ILD histological pattern, present in up to 77% of cases, although UIP can also be seen in 25–40% of cases.^{93,100}

Typically SSc-ILD manifests on HRCT as predominantly ground-glass opacities (GGO) with a combination of pulmonary fibrosis, consistent with the NSIP pattern, which can be subcategorized as cellular NSIP or fibrotic NSIP.¹⁰¹ Fibrotic NSIP is more prevalent than the cellular subtype and has higher risk of progression.¹⁰² However, honeycombing cystic change is reported between 11 and 37% of patients with SSc-ILD.^{99,103} Since the honeycombing pattern is typically a marker for UIP and pulmonary fibrosis and is rarely present in NSIP pattern, it is suggested that patients with SSc-ILD may have an overlap of different patterns. Table 1 shows the radiological patterns and signs of fibrosis on chest HRCT.¹⁰⁴

Chest HRCT is the main tool to detect and to characterize ILD in SSc. Examples of the NSIP pattern with different radiological signs in patients with SSc are shown in Figs. 1–4. As previously noted, it is highly recommended that HRCT be performed in all patients with SSc at the beginning of the

Table 1 – Radiological patterns and signs of fibrosis on chest high resolution computed tomography.

Radiological patterns	Radiological signs
NSIP	• Peripheral distribution; occasionally central • Preference in inferior lobes • Patchy GGO with linear, reticular, and micronodular images • Traction bronchiectasis/bronchiolectasis when NSIP fibrotic • Infrequent honeycombing cystic pattern
UIP	• Subpleural, basal and symmetrical; occasionally diffuse • Apico-basal progression • Honeycombing pattern with reticulation, bronchiectasis, and traction bronchiectasis • Minimal ground-glass opacities
LIP	• Bilateral involvement • Preference in inferior lobes • Patchy areas of GGO with small centrilobular unclearly defined nodules • Multiple thin-walled cysts
OP	• Peripheral and often frankly subpleural • Patchy areas of consolidation (increased lung attenuation with architectural distortion) • Coalescence progression to diffuse alveolar damage and fibrosis signs with GGO and traction bronchiectasis

Definition of abbreviations: NSIP=non-specific interstitial pneumonia; GGO=ground glass opacities; UIP=usual interstitial pneumonia; LIP=lymphoid interstitial pneumonia; OP=organizing pneumonia.

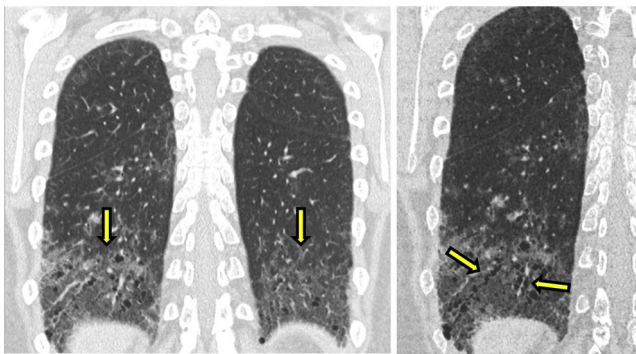


Fig. 4 – (A) Fibrotic NSIP with lower bilateral ground-glass opacities (arrows) and (B) multiple traction bronchiectasis (arrows).

disease.¹⁰⁵ HRCT is also useful for the assessment of disease progression. Several studies demonstrated that patients with UIP pattern tend to have worst survival in comparison with patients with NSIP pattern.⁹⁸

Prognosis and risk factors

While the ILD pattern on HRCT is useful for diagnosis, and there is a trend for shorter survival in patients with UIP pattern compared to those with an NSIP pattern,⁹⁸ the utility of assessing SSc-ILD prognosis on the basis of pattern alone is limited. In contrast, to HRCT patterns, fibrotic findings have been correlated with mortality in SSc. A recent study of the Norwegian nationwide SSc cohort found an association between the presence of fibrosis and mortality.⁹⁰ We can find fibrotic features in 55–65% of all patients with SSc and in up to 96% of those with abnormal pulmonary function test (PFT) results.⁹⁹

The extent of parenchymal involvement on HRCT is an important outcome measure. Several studies analyzed the visual scoring of lung fibrosis extent and demonstrated that more extensive ILD (>20% of lung tissue involved) was associated with decreased survival.^{83,106} Subsequently, numerous studies have demonstrated a significant correlation between the progression of ILD extent on HRCT scan over time and the decline of predicted DLCO, but only a trend for FVC.^{107–109} However, there is a low degree of agreement on the quantification of the ILD extent among expert radiologists.

Recently, the use of quantitative CT (QCT) methods have been evaluated to improve diagnostic accuracy, and several studies have shown them to be a powerful tool in the evaluation of connective tissue-related ILD and specifically scleroderma-related ILD.¹¹⁰ Different quantitative analysis tools have shown to produce objective, quantifiable and reproducible assessments of disease progression and stratification. The CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) platform is a useful tool not only to quantify lung damage but also to evaluate the worsening of PFTs, as it showed that a value of ground glass $\geq 4.5\%$ is predictive of DLCO worsening of 10%.¹¹¹

The combination of pulmonary fibrosis and emphysema (CPFE syndrome) has been reported in patients with CTD-ILD.^{112,113} A study including a cohort of >300 patients found a significant prevalence of emphysema in patients with SSc-ILD in both smokers and nonsmokers.¹¹² Emphysema was associated, for a given extent of fibrosis, with a reduction in DLCO of >10%.¹¹²

In SSc-ILD, the clinical course of disease varies widely from slowly progressive, or even stable disease, to severe and rapidly progressing.¹¹⁴ The prognosis for patients is more closely linked to a combination of severity indicators including progressive functional decline and disease extent of lung fibrosis by HRCT, together with other clinical and laboratory variables.^{84,115–117}

Careful prognostic evaluation is essential to the formulation of a management plan, including the staging of disease severity and the definition of longitudinal disease behavior (by serial imaging and PFT).⁸⁵

Pulmonary function tests (PFTs) have been associated with an increased risk of mortality¹¹⁸⁻¹²⁰ in SSc-ILD. A *post hoc* Cox regression analysis of patients from SLS I and II showed that significant declines in FVC ($\geq 10\%$ predicted) or DLCO ($\geq 15\%$ predicted) over 24 months were strong prognosis factors as predictors of mortality, even when adjusting for treatment arm and baseline disease severity.¹²¹ PFT was added to the Outcome Measures in Rheumatology (OMERACT) definition of progression of CTD-ILD. A clinically meaningful progression was defined as: $\geq 10\%$ relative decline in %FVC predicted or 5–10% relative decline in %FVC and $\geq 15\%$ relative decline in %DLCO predicted.¹²²

Additional risk factors for worse prognosis of SSc-ILD include demographic (male sex, older age, African American race, smoking habits) and clinical involvements (absence or presence of respiratory symptoms, arthritis, diffuse SSc subtype with elevated Rodnan skin score, gastro-esophageal reflux disease, pulmonary hypertension), specific antibodies (anti-Scl70 and RNA-polIII) and circulating biomarkers such as elevated C-reactive protein.^{93,121-124} The skin is almost always involved in systemic sclerosis, and several studies have shown that there is an increased risk of ILD and progression of ILD-SSc in presence of diffuse skin involvement.^{93,120,125-127} On the other hand, the presence of anti-centromere antibodies decreases the likelihood to develop ILD.^{105,128}

Gastro-esophageal reflux (GERD) is another clinical manifestation recognized as a potential risk impairing lung function in SSc-ILD.^{129,130}

Circulating biomarkers have long been associated with the presence and development of SSc-ILD, but their potential to classify ILD and to predict the clinical course of the disease is to date conflicting and their use is not yet validated for management of SSc-ILD in clinical practice.^{93,105} Currently, Krebs von der Lungen-6 serum level (sKL-6) is considered to be one of the most reliable biomarkers for diagnosis, prognosis and prediction of therapeutic responsiveness of SSc-ILD. In SSc-ILD, sKL-6 has been found to be negatively correlated with pulmonary function and positively correlated with radiological extent of lung fibrosis.¹³¹ Furthermore, sKL-6 > 1000 U/mL was associated with increased mortality at 5 years of follow-up.¹³² The serum values for surfactant protein-A (SP-A) and D (SP-D) have been associated with the extent of damage to the capillary/alveolar barrier, but their diagnostic and prognostic value in SSc-ILD is still controversial.¹³³ SP-A is known to have lower sensitivity and specificity than SP-D. SP-D appeared to be a strong biomarker for diagnosis.¹³¹ It also is associated with severity of SSc-ILD,¹³⁴ correlating significantly with fibrosis scores on HRCT but not with ground-glass opacities.¹³¹ Another promising biomarker for activity and severity of SSc-ILD is the serum level of CCL18 (Pulmonary and Activation Regulated Chemokine (PARC)), which was found to be a predictor of mortality and progression.^{135,136} A large prospective trial with 427 patients with SSc-ILD showed that sCCL18 > 85 pg/mL and male sex were the best predictors of functional decline,¹³¹ although the association with mortality was unclear.

Unmet needs and prediction models

Personalized medicine and a multidisciplinary approach are essential to stage the severity of the disease and to determine the likelihood of progression. The current evidence from observational cohorts suggest that only 20–30% of patients with SSc-ILD will develop a progressive disease course.¹³⁷⁻¹³⁹ Accurately assessing and defining progression in SSc-ILD could help identify patients at risk. Accordingly, different composite grading systems for screening and prognosis of ILD in SSc have been proposed. Goh et al. developed an algorithm in order to classify patients based on the extent of disease⁸³ integrating HRCT observations and FVC values from PFTs. Extensive disease was defined as: $> 20\%$ lung involvement on HRCT or 10–20% lung involvement on HRCT and FVC $< 70\%$ predicted. On the other hand, limited disease was defined as: $\leq 10\%$ lung involvement on HRCT, or 10–20% lung involvement on HRCT and FVC $\geq 70\%$ predicted. This prognostic algorithm has been validated as a predictor of mortality. There is an approximately a three-fold increased risk of death and clinical decline (defined as need for supplemental oxygen or lung transplantation) in patients with SSc-ILD how have extensive disease compared to those with limited disease.¹¹⁸⁻¹²⁰

The SPAR model was suggested in 2018 as a useful composite staging system to predict ILD progression by combining SpO₂ after 6MWT (6-minute walk test) and the presence of arthritis (defined as one or more tender and swollen joints as judged by the treating physician).¹⁴⁰ Wu et al. developed this model by using two independent prospective cohorts of patients who met 2013 ACR/EULAR Classification Criteria for SSc and had mild ILD ($< 20\%$ lung involvement) assessed by HRCT at baseline. It defined ILD progression as a decrease in FVC $\geq 15\%$ or $\geq 10\%$ combined with a decrease in DLCO $\geq 15\%$ at 1-year follow-up. In their multivariate analysis, declines in SpO₂ after 6MWT and arthritis were identified in both cohorts as independent predictors of ILD progression, with an optimal SpO₂ cut-off value of 94% by receiver–operator characteristic analysis. A latter observational study demonstrated that the SPAR model increased the prediction success rate for ILD progression to 91.7% among patients who fulfilled criteria for both the SpO₂ $\leq 94\%$ after 6MWT and arthritis.

Another validated prediction model for mortality risk in SSc-ILD is the smoking history, age, and DLCO (SADL) model, which was developed by using two independent prospective cohorts of patients meeting 2013 ACR/EULAR Criteria for ILD. The three abovementioned variables were included in the final risk prediction model to create a point scoring system used to identify a classification with low, moderate or high mortality risk at Three years from ILD diagnosis.¹⁴¹

Including simple commonly used variables facilitates the use of these composite-staging systems, which can be useful tools in clinical practice, even though further validation is required.

Progressive pulmonary fibrosis

Recently, progressive pulmonary fibrosis (PPF), also referred to as progressive fibrosing ILDs (PF-ILD), was recognized as a

Table 2 – Definition of progressive pulmonary fibrosis.

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation^a:

1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following):
 - a. Absolute decline in FVC $\geq$ 5% predicted within 1 year of follow-up
 - b. Absolute decline in DLCO (corrected for Hb) $\geq$ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression (one or more of the following):
 - a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
 - b. New ground-glass opacity with traction bronchiectasis
 - c. New fine reticulation
 - d. Increased extent or increased coarseness of reticular abnormality
 - e. New or increased honeycombing
 - f. Increased lobar volume loss

Definition of abbreviations: ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; PPF=progressive pulmonary fibrosis; Hb=hemoglobin.

^a Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, that is particularly important in patients with worsening respiratory symptoms and/or decline in DLCO given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

distinct clinical entity^{101,142} by the American Thoracic Society and European Respiratory Society/ATS/ERS) in collaboration with the American College of Chest Physicians (ACCP). The established definition of PPF is shown in Table 2.¹⁰¹

Accordingly, PPF is characterized by a disease course like that of idiopathic pulmonary fibrosis (IPF), the prototype of fibrosing ILD, with rapid decline in lung function, respiratory failure, and higher infection risk due to an increased distal alveolar bacterial burden, leading to early mortality. Therefore, it is crucial to monitor the evolution of SSc-ILD, and should rely on multicompartamental assessment (physiological, clinical, and radiological assessment, together with validated biomarkers).

In addition, non-lethal complications of SSc could often be of greater importance to patients than the risk of developing a life-threatening lung manifestation and so a comprehensive, multidisciplinary long-term care plan must provide the context for management of organ-based disease. The recent European consensus statement¹⁰⁵ showed support for a multidimensional model of care and proposed an algorithm to provide clinical guidance for the identification and management of SSc-ILD, assessing ILD severity by using multiple methods (HRCT, FVC and DLCO, exercise-induced blood oxygen desaturation, clinical symptoms, and quality of life).

Conclusions

In SSc, the early identification of ILD is of paramount importance for prompt initiation of disease management strategies and therapies to slow and hopefully arrest disease evolution. Screening is pivotal and should be regularly conducted early in the SSc disease course in all patients. The gold standard for ILD diagnosis is HRCT, a technique that is associated with radiation exposure and can be burdensome to organize as well as costs. For this reason, the combination of PFTs and lung ultrasound may emerge as a viable approach that can be repeated on multiple occasions without radiation concern. Currently, conclusive diagnosis relies on HRCT with characterization of the architectural features of the lung that also point

at the possible pathological pattern. In follow-up, clinical signs and symptoms as well as PFTs and HRCT are instrumental to define disease progression and shape tailored treatment for each SSc patient.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:[10.1016/j.rcreu.2023.09.001](https://doi.org/10.1016/j.rcreu.2023.09.001).

REFERENCES

1. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69:1809–15, <http://dx.doi.org/10.1136/ard.2009.114264>.
2. Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk AP, et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. *Ann Rheum Dis*. 2009;68:961–5, <http://dx.doi.org/10.1136/ard.2008.091710>.
3. Steele R, Hudson M, Lo E, Baron M. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2012;64:519–24, <http://dx.doi.org/10.1002/acr.21583>.
4. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J Respir Crit Care Med*. 2020;201:650–60, <http://dx.doi.org/10.1164/rccm.201903-0563CI>.
5. Nihtyanova SI, Denton CP. Pathogenesis of systemic sclerosis associated interstitial lung disease. *J Scleroderma Relat Disord*. 2020;5 Suppl.:6–16, <http://dx.doi.org/10.1177/2397198320903867>.
6. Akter T, Silver RM, Bogatkevich GS. Recent advances in understanding the pathogenesis of scleroderma-interstitial

- lung disease. *Curr Rheumatol Rep.* 2014;16:411, <http://dx.doi.org/10.1007/s11926-014-0411-1>.
7. Ostojic P, Cerinic MM, Silver R, Highland K, Damjanov N. Interstitial lung disease in systemic sclerosis. *Lung.* 2007;185:211–20, <http://dx.doi.org/10.1007/s00408-007-9012-3>.
 8. Ohba T, McDonald JK, Silver RM, Strange C, LeRoy EC, Ludwicka A. Scleroderma bronchoalveolar lavage fluid contains thrombin, a mediator of human lung fibroblast proliferation via induction of platelet-derived growth factor alpha-receptor. *Am J Respir Cell Mol Biol.* 1994;10:405–12, <http://dx.doi.org/10.1165/ajrcmb.10.4.7510986>.
 9. Ludwicka-Bradley A, Silver RM, Bogatkevich GS. Coagulation and autoimmunity in scleroderma interstitial lung disease. *Semin Arthritis Rheum.* 2011;41:212–22, <http://dx.doi.org/10.1016/j.semarthrit.2010.10.002>.
 10. Bogatkevich GS, Ludwicka-Bradley A, Silver RM. Dabigatran, a direct thrombin inhibitor, demonstrates antifibrotic effects on lung fibroblasts. *Arthritis Rheum.* 2009;60:3455–64, <http://dx.doi.org/10.1002/art.24935>.
 11. Bogatkevich GS, Ludwicka-Bradley A, Nietert PJ, Akter T, van Ryn J, Silver RM. Antiinflammatory and antifibrotic effects of the oral direct thrombin inhibitor dabigatran etexilate in a murine model of interstitial lung disease. *Arthritis Rheum.* 2011;63:1416–25, <http://dx.doi.org/10.1002/art.30255>.
 12. Silver RM, Wilson DA, Akter T, Atanelishvili I, Huggins JT, Kajdasz K, et al. Safety and tolerability of thrombin inhibition in scleroderma-associated interstitial lung disease. *ACR Open Rheumatol.* 2019;1:403–11, <http://dx.doi.org/10.1002/acr2.11049>.
 13. Silver RM. Endothelin and scleroderma lung disease. *Rheumatology (Oxford).* 2008;47 Suppl. 5:v25–6, <http://dx.doi.org/10.1093/rheumatology/ken283>.
 14. Odoux C, Crestani B, Lebrun G, Rolland C, Aubin P, Seta N, et al. Endothelin-1 secretion by alveolar macrophages in systemic sclerosis. *Am J Respir Crit Care Med.* 1997;156:1429–35, <http://dx.doi.org/10.1164/ajrccm.156.5.96-11004>.
 15. Wermuth PJ, Li Z, Mendoza FA, Jimenez SA. Stimulation of transforming growth factor- β 1-induced endothelial-to-mesenchymal transition and tissue fibrosis by endothelin-1 (ET-1): a novel profibrotic effect of ET-1. *PLOS ONE.* 2016;11:e0161988, <http://dx.doi.org/10.1371/journal.pone.0161988>.
 16. Abraham DJ, Vancheeswaran R, Dashwood MR, Rajkumar VS, Pantelides P, Xu SW, et al. Increased levels of endothelin-1 and differential endothelin type A and B receptor expression in scleroderma-associated fibrotic lung disease. *Am J Pathol.* 1997;151:831–41.
 17. Pulito-Cueto V, Genre F, López-Mejías R, Mora-Cuesta VM, Iturbe-Fernández D, Portilla V, et al. Endothelin-1 as a biomarker of idiopathic pulmonary fibrosis and interstitial lung disease associated with autoimmune diseases. *Int J Mol Sci.* 2023;24, <http://dx.doi.org/10.3390/ijms24021275>.
 18. Cambrey AD, Harrison NK, Dawes KE, Southcott AM, Black CM, du Bois RM, et al. Increased levels of endothelin-1 in bronchoalveolar lavage fluid from patients with systemic sclerosis contribute to fibroblast mitogenic activity in vitro. *Am J Respir Cell Mol Biol.* 1994;11:439–45, <http://dx.doi.org/10.1165/ajrcmb.11.4.7917311>.
 19. Vancheeswaran R, Magoulas T, Efrat G, Wheeler-Jones C, Olsen I, Penny R, et al. Circulating endothelin-1 levels in systemic sclerosis subsets – a marker of fibrosis or vascular dysfunction? *J Rheumatol.* 1994;21:1838–44.
 20. Guillén-Del-Castillo A, Simeón-Aznar CP, Callejas-Moraga EL, Tolosa-Vilella C, Alonso-Vila S, Fonollosa-Pla V, et al. Quantitative videocapillaroscopy correlates with functional respiratory parameters: a clue for vasculopathy as a pathogenic mechanism for lung injury in systemic sclerosis. *Arthritis Res Ther.* 2018;20:281, <http://dx.doi.org/10.1186/s13075-018-1775-9>.
 21. Mason RJ, Williams MC. Type II alveolar cell. Defender of the alveolus. *Am Rev Respir Dis.* 1977;115 Pt 2:81–91.
 22. Doskaliuk B, Zaiats L, Yatsyshyn R, Gerych P, Cherniuk N, Zimba O. Pulmonary involvement in systemic sclerosis: exploring cellular, genetic and epigenetic mechanisms. *Rheumatol Int.* 2020;40:1555–69, <http://dx.doi.org/10.1007/s00296-020-04658-6>.
 23. Bonhomme O, André B, Gester F, de Seny D, Moermans C, Struman I, et al. Biomarkers in systemic sclerosis-associated interstitial lung disease: review of the literature. *Rheumatology (Oxford).* 2019;58:1534–46, <http://dx.doi.org/10.1093/rheumatology/kez230>.
 24. Ohshimo S, Yokoyama A, Hattori N, Ishikawa N, Hirasawa Y, Kohno N. KL-6, a human MUC1 mucin, promotes proliferation and survival of lung fibroblasts. *Biochem Biophys Res Commun.* 2005;338:1845–52, <http://dx.doi.org/10.1016/j.bbrc.2005.10.144>.
 25. Stock CJW, Hoyles RK, Daccord C, Kokosi M, Visca D, De Lauretis A, et al. Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. *Respirology.* 2021;26:461–8, <http://dx.doi.org/10.1111/resp.13988>.
 26. Hesselstrand R, Wildt M, Bozovic G, Andersson-Sjöland A, Andréasson K, Scheja A, et al. Biomarkers from bronchoalveolar lavage fluid in systemic sclerosis patients with interstitial lung disease relate to severity of lung fibrosis. *Respir Med.* 2013;107:1079–86, <http://dx.doi.org/10.1016/j.rmed.2013.03.015>.
 27. Willis BC, Borok Z. TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease. *Am J Physiol Lung Cell Mol Physiol.* 2007;293:L525–34, <http://dx.doi.org/10.1152/ajplung.00163.2007>.
 28. Corrin B, Butcher D, McAnulty BJ, Dubois RM, Black CM, Laurent GJ, et al. Immunohistochemical localization of transforming growth factor-beta 1 in the lungs of patients with systemic sclerosis, cryptogenic fibrosing alveolitis and other lung disorders. *Histopathology.* 1994;24:145–50, <http://dx.doi.org/10.1111/j.1365-2559.1994.tb01293.x>.
 29. Hashimoto N, Phan SH, Imaizumi K, Matsuo M, Nakashima H, Kawabe T, et al. Endothelial-mesenchymal transition in bleomycin-induced pulmonary fibrosis. *Am J Respir Cell Mol Biol.* 2010;43:161–72, <http://dx.doi.org/10.1165/rcmb.2009-0031OC>.
 30. Mendoza FA, Piera-Velazquez S, Farber JL, Feghali-Bostwick C, Jiménez SA. Endothelial cells expressing endothelial and mesenchymal cell gene products in lung tissue from patients with systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol.* 2016;68:210–7, <http://dx.doi.org/10.1002/art.39421>.
 31. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med.* 2012;185:1004–14, <http://dx.doi.org/10.1165/rcmb.201202-0320ST>.
 32. Orlandi M, Meliante LA, Damiani A, Tofani L, Bruni C, Guiducci S, et al. The role of bronchoalveolar lavage in systemic sclerosis interstitial lung disease: a systematic literature review. *Pharmaceuticals (Basel).* 2022;15, <http://dx.doi.org/10.3390/ph15121584>.
 33. Harrison NK, McAnulty RJ, Haslam PL, Black CM, Laurent GJ. Evidence for protein oedema, neutrophil influx, and enhanced collagen production in lungs of patients with systemic sclerosis. *Thorax.* 1990;45:606–10, <http://dx.doi.org/10.1136/thx.45.8.606>.

34. Harrison NK, Myers AR, Corrin B, Soosay G, Dewar A, Black CM, et al. Structural features of interstitial lung disease in systemic sclerosis. *Am Rev Respir Dis*. 1991;144 Pt 1:706-13, <http://dx.doi.org/10.1164/ajrccm/144.3.Pt.1.706>.
35. da Silva SO, da Paz AS, Farias I, Moreira DS, Ribeiro MAF, Alves T, et al. Bronchoalveolar lavage in systemic sclerosis patients: a systematic review. *Curr Rheumatol Rev*. 2021;17:176-83, <http://dx.doi.org/10.2174/1573397116666201113091655>.
36. Schmidt K, Martinez-Gamboa L, Meier S, Witt C, Meisel C, Hanitsch LG, et al. Bronchoalveolar lavage fluid cytokines and chemokines as markers and predictors for the outcome of interstitial lung disease in systemic sclerosis patients. *Arthritis Res Ther*. 2009;11:R111, <http://dx.doi.org/10.1186/ar2766>.
37. Becker MO, Radic M, Schmidt K, Huscher D, Riedlinger A, Michelfelder M, et al. Serum cytokines and their predictive value in pulmonary involvement of systemic sclerosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2019;36:274-84.
38. Kowal-Bielecka O, Distler O, Kowal K, Siergiejko Z, Chwiećko J, Sulik A, et al. Elevated levels of leukotriene B4 and leukotriene E4 in bronchoalveolar lavage fluid from patients with scleroderma lung disease. *Arthritis Rheum*. 2003;48:1639-46, <http://dx.doi.org/10.1002/art.11042>.
39. Khadilkar PV, Khopkar US, Nadkar MY, Rajadhyaksha AG, Chougule DA, Deshpande SD, et al. Fibrotic cytokine interplay in evaluation of disease activity in treatment naïve systemic sclerosis patients from Western India. *J Assoc Physicians India*. 2019;67:26-30.
40. O'Reilly S, Hügle T, van Laar JM. T cells in systemic sclerosis: a reappraisal. *Rheumatology (Oxford)*. 2012;51:1540-9, <http://dx.doi.org/10.1093/rheumatology/kes090>.
41. Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. *Eur Respir Rev*. 2015;24:102-14, <http://dx.doi.org/10.1183/09059180.00003214>.
42. Versace AG, Bitto A, Ioppolo C, Aragona CO, La Rosa D, Roberts WN, et al. IL-13 and IL-33 Serum levels are increased in systemic sclerosis patients with interstitial lung disease. *Front Med (Lausanne)*. 2022;9:825567, <http://dx.doi.org/10.3389/fmed.2022.825567>.
43. Truchetet ME, Brembilla NC, Montanari E, Allanore Y, Chizzolini C. Increased frequency of circulating Th22 in addition to Th17 and Th2 lymphocytes in systemic sclerosis: association with interstitial lung disease. *Arthritis Res Ther*. 2011;13:R166, <http://dx.doi.org/10.1186/ar3486>.
44. Kardum Ž, Milas-Ahić J, Šahinović I, Masle AM, Uršić D, Kos M. Serum levels of interleukin 17 and 22 in patients with systemic sclerosis: a single-center cross-sectional study. *Rheumatol Int*. 2023;43:345-54, <http://dx.doi.org/10.1007/s00296-022-05250-w>.
45. Frantz C, Auffray C, Avouac J, Allanore Y. Regulatory T cells in systemic sclerosis. *Front Immunol*. 2018;9:2356, <http://dx.doi.org/10.3389/fimmu.2018.02356>.
46. Jiang N, Li M, Zeng X. Correlation of Th17 cells and CD4⁺CD25⁺ regulatory T cells with clinical parameters in patients with systemic sclerosis. *Chin Med J (Engl)*. 2014;127:3557-61.
47. Luo J, Li D, Jiang L, Shi C, Duan L. Identification of tregs-related genes with molecular patterns in patients with systemic sclerosis related to ILD. *Biomolecules*. 2023;13, <http://dx.doi.org/10.3390/biom13030535>.
48. Tang J, Lei L, Pan J, Zhao C, Wen J. Higher levels of serum interleukin-35 are associated with the severity of pulmonary fibrosis and Th2 responses in patients with systemic sclerosis. *Rheumatol Int*. 2018;38:1511-9, <http://dx.doi.org/10.1007/s00296-018-4071-8>.
49. Radstake TR, van Bon L, Broen J, Wenink M, Santegoets K, Deng Y, et al. Increased frequency and compromised function of T regulatory cells in systemic sclerosis (SSc) is related to a diminished CD69 and TGFbeta expression. *PLoS ONE*. 2009;4:e5981, <http://dx.doi.org/10.1371/journal.pone.0005981>.
50. Ugor E, Simon D, Almanzar G, Pap R, Najbauer J, Németh P, et al. Increased proportions of functionally impaired regulatory T cell subsets in systemic sclerosis. *Clin Immunol*. 2017;184:54-62, <http://dx.doi.org/10.1016/j.clim.2017.05.013>.
51. O'Reilly S. Role of interleukin-13 in fibrosis, particularly systemic sclerosis. *Biofactors*. 2013;39:593-6, <http://dx.doi.org/10.1002/biof.1117>.
52. Shi W, Zhou H, Zhu X, Xie J, Huang Z. The association of IL-33 and systemic sclerosis: a systematic review and meta-analysis. *Immunol Res*. 2023;71:60-9, <http://dx.doi.org/10.1007/s12026-022-09329-1>.
53. Pellicano C, Iannazzo F, Romaggioli L, Rosato E. IL33 and sST2 serum level in systemic sclerosis microvascular involvement. *Microvasc Res*. 2022;142:104344, <http://dx.doi.org/10.1016/j.mvr.2022.104344>.
54. Yanaba K, Yoshizaki A, Asano Y, Kadono T, Sato S. Serum IL-33 levels are raised in patients with systemic sclerosis: association with extent of skin sclerosis and severity of pulmonary fibrosis. *Clin Rheumatol*. 2011;30:825-30, <http://dx.doi.org/10.1007/s10067-011-1686-5>.
55. Beesley CF, Goldman NR, Taher TE, Denton CP, Abraham DJ, Mageed RA, et al. Dysregulated B cell function and disease pathogenesis in systemic sclerosis. *Front Immunol*. 2022;13:999008, <http://dx.doi.org/10.3389/fimmu.2022.999008>.
56. Lafyatis R, O'Hara C, Feghali-Bostwick CA, Matteson E. B cell infiltration in systemic sclerosis-associated interstitial lung disease. *Arthritis Rheum*. 2007;56:3167-8, <http://dx.doi.org/10.1002/art.22847>.
57. Bouaziz JD, Calbo S, Maho-Vaillant M, Saussine A, Bagot M, Bensussan A, et al. IL-10 produced by activated human B cells regulates CD4(+) T-cell activation in vitro. *Eur J Immunol*. 2010;40:2686-91, <http://dx.doi.org/10.1002/eji.201040673>.
58. Matsushita T, Hamaguchi Y, Hasegawa M, Takehara K, Fujimoto M. Decreased levels of regulatory B cells in patients with systemic sclerosis: association with autoantibody production and disease activity. *Rheumatology (Oxford)*. 2016;55:263-7, <http://dx.doi.org/10.1093/rheumatology/kev331>.
59. Mavropoulos A, Simopoulou T, Varna A, Liaskos C, Katsiari CG, Bogdanos DP, et al. Breg cells are numerically decreased and functionally impaired in patients with systemic sclerosis. *Arthritis Rheumatol*. 2016;68:494-504, <http://dx.doi.org/10.1002/art.39437>.
60. Horii M, Fushida N, Ikeda T, Oishi K, Hamaguchi Y, Ikawa Y, et al. Cytokine-producing B-cell balance associates with skin fibrosis in patients with systemic sclerosis. *J Dermatol*. 2022;49:1012-9, <http://dx.doi.org/10.1111/1346-8138.16495>.
61. Lin X, Ding M, Chen T, Min S, Wang D, Jiang G. Peripheral blood IL-6 levels in systemic sclerosis patients: correlation between IL-6 levels and clinical phenotypes. *J Cosmet Dermatol*. 2022;21:6086-91, <http://dx.doi.org/10.1111/jocd.15133>.
62. De Lauretis A, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NS, et al. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J Rheumatol*. 2013;40:435-46, <http://dx.doi.org/10.3899/jrheum.120725>.
63. Wu M, Mohan C. B-cells in systemic sclerosis: emerging evidence from genetics to phenotypes. *Curr Opin Rheumatol*. 2015;27:537-41, <http://dx.doi.org/10.1097/BOR.0000000000000215>.

64. Cavazzana I, Vojinovic T, Airo P, Fredi M, Ceribelli A, Pedretti E, et al. Systemic sclerosis-specific antibodies: novel and classical biomarkers. *Clin Rev Allergy Immunol*. 2023;64:412–30, <http://dx.doi.org/10.1007/s12016-022-08946-w>.
65. Ludwicka A, Trojanowska M, Smith EA, Baumann M, Strange C, Korn JH, et al. Growth and characterization of fibroblasts obtained from bronchoalveolar lavage of patients with scleroderma. *J Rheumatol*. 1992;19:1716–23.
66. Kreuter M, Hoffmann-Vold AM, Matucci-Cerinic M, Saketkoo LA, Highland KB, Wilson H, et al. Impact of lung function and baseline clinical characteristics on patient-reported outcome measures in systemic sclerosis-associated interstitial lung disease. *Rheumatology (Oxford)*. 2023;62:Si43–53, <http://dx.doi.org/10.1093/rheumatology/keac325>.
67. Hoffmann-Vold A-M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol*. 2020;2:e71–83.
68. Showalter K, Hoffmann A, Rouleau G, Aaby D, Lee J, Richardson C, et al. Performance of forced vital capacity and lung diffusion cutpoints for associated radiographic interstitial lung disease in systemic sclerosis. *J Rheumatol*. 2018;45:1572–6, <http://dx.doi.org/10.3899/jrheum.171362>.
69. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TD, Maurer B, Jordan S, et al. Brief report: pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. *Arthritis Rheumatol*. 2015;67:3256–61, <http://dx.doi.org/10.1002/art.39405>.
70. Bernstein EJ, Jaafar S, Assassi S, Domsic RT, Frech TM, Gordon JK, et al. Performance characteristics of pulmonary function tests for the detection of interstitial lung disease in adults with early diffuse cutaneous systemic sclerosis. *Arthritis Rheumatol*. 2020;72:1892–6, <http://dx.doi.org/10.1002/art.41415>.
71. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. *PLOS ONE*. 2016;11:e0163894, <http://dx.doi.org/10.1371/journal.pone.0163894>.
72. Tashkin DP, Volkmann ER, Tseng CH, Kim HJ, Goldin J, Clements P, et al. Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. *Ann Rheum Dis*. 2016;75:374–81, <http://dx.doi.org/10.1136/annrheumdis-2014-206076>.
73. Bernstein EJ, Khanna D, Lederer DJ. Screening high-resolution computed tomography of the chest to detect interstitial lung disease in systemic sclerosis: a global survey of rheumatologists. *Arthritis Rheumatol*. 2018;70:971–2, <http://dx.doi.org/10.1002/art.40441>.
74. Khanna D, Lescoat A, Roofeh D, Bernstein EJ, Kazerooni EA, Roth MD, et al. Systemic sclerosis-associated interstitial lung disease: how to incorporate two food and drug administration-approved therapies in clinical practice. *Arthritis Rheumatol*. 2022;74:13–27, <http://dx.doi.org/10.1002/art.41933>.
75. Roofeh D, Jaafar S, Vummidi D, Khanna D. Management of systemic sclerosis-associated interstitial lung disease. *Curr Opin Rheumatol*. 2019;31:241–9, <http://dx.doi.org/10.1097/BOR.0000000000000592>.
76. Bruni C, Chung L, Hoffmann-Vold AM, Assassi S, Gabrielli A, Khanna D, et al. High-resolution computed tomography of the chest for the screening, re-screening and follow-up of systemic sclerosis-associated interstitial lung disease: a EUSTAR-SCTC survey. *Clin Exp Rheumatol*. 2022;40:1951–5, <http://dx.doi.org/10.55563/clinexprheumatol/7ry6zz>.
77. Bernstein EJ, Assassi S, Castellino FV, Chung L, Correia C, Evnin LB, et al. Computed tomography of the chest to screen for interstitial lung disease in patients with systemic sclerosis at expert scleroderma centers in the United States. *ACR Open Rheumatol*. 2022;4:596–602, <http://dx.doi.org/10.1002/acr2.11434>.
78. Rahaghi FF, Hsu VM, Kaner RJ, Mayes MD, Rosas IO, Saggat R, et al. Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. *Respir Res*. 2023;24:6, <http://dx.doi.org/10.1186/s12931-022-02292-3>.
79. Gomes Guerra M, Machado Pinto T, Águeda A, Rodrigues J, Marona J, Violante A, et al. The role of lung ultrasound in systemic sclerosis: a systematic review. *J Clin Rheumatol*. 2023;29:e32–9, <http://dx.doi.org/10.1097/RHU.0000000000001947>.
80. Radić M, Đogaš H, Gelemanović A, Jurić Petričević S, Škopljanać I, Radić J. Pulmonary ultrasonography in systemic sclerosis-induced interstitial lung disease – a systematic review and meta-analysis. *Diagnostics (Basel)*. 2023;13, <http://dx.doi.org/10.3390/diagnostics13081429>.
81. Fairchild R, Chung M, Yang D, Sharpless L, Li S, Chung L. Development and assessment of novel lung ultrasound interpretation criteria for the detection of interstitial lung disease in systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2021;73:1338–42, <http://dx.doi.org/10.1002/acr.24338>.
82. Gargani L, Romei C, Bruni C, Lepri G, El-Aoufy K, Orlandi M, et al. Lung ultrasound B-lines in systemic sclerosis: cut-off values and methodological indications for interstitial lung disease screening. *Rheumatology (Oxford)*. 2022;61(Si):Si56–64, <http://dx.doi.org/10.1093/rheumatology/keab801>.
83. Goh NSL, Desai SR, Veeraraghavan S, Hansell DMM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med*. 2008;177:1248–54, <http://dx.doi.org/10.1164/rccm.200706-877OC>.
84. Denton CP, Wells AU, Coghlan JG. Major lung complications of systemic sclerosis. *Nat Rev Rheumatol*. 2018;14:511–27, <http://dx.doi.org/10.1038/s41584-018-0062-0>.
85. Varga J, Denton CP, Wigley FM. Scleroderma. From pathogenesis to comprehensive management. Springer International Publishing; 2012. p. 415–8, <http://dx.doi.org/10.1007/978-1-4419-5774-0>.
86. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69:1809–15, <http://dx.doi.org/10.1136/ard.2009.114264>.
87. Khanna D, Nagaraja V, Tseng C, Abtin F, Suh R, Kim G, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. *Arthritis Res Ther*. 2015;17:1–10, <http://dx.doi.org/10.1186/s13075-015-0872-2>.
88. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390:1685–99, [http://dx.doi.org/10.1016/S0140-6736\(17\)30933-9](http://dx.doi.org/10.1016/S0140-6736(17)30933-9).
89. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TDL, Maurer B, Jordan S, et al. Pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. *Arthritis Rheumatol*. 2015;67:3256–61, <http://dx.doi.org/10.1002/art.39405>.
90. Hoffmann-Vold A, Fretheim H, Halse A, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung

- disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med*. 2019;200:1258–66, <http://dx.doi.org/10.1164/rccm.201903-0486OC>.
91. Molberg Ø, Hoffmann-Vold AM. Interstitial lung disease in systemic sclerosis: progress in screening and early diagnosis. *Curr Opin Rheumatol*. 2016;28:613–8, <http://dx.doi.org/10.1097/BOR.0000000000000323>.
 92. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med*. 2020;383:958–68, <http://dx.doi.org/10.1056/NEJMr2005230>.
 93. Molina-Molina M, Castellví I, Valenzuela C, Ramirez J, Rodríguez Portal JA, Franquet T, et al. Management of progressive pulmonary fibrosis associated with connective tissue disease. *Expert Rev Respir Med*. 2022;16:765–74, <http://dx.doi.org/10.1080/17476348.2022.2107508>.
 94. Aburto M, Herráez I, Iturbe D, Jiménez-Romero A. Diagnosis of idiopathic pulmonary fibrosis: differential diagnosis. *Med Sci*. 2018;6:73, <http://dx.doi.org/10.3390/medsci6030073>.
 95. Hinchcliff M, Khanna S, Hsu VM, Lee J, Almagor O, Chang RW, et al. Survival in systemic sclerosis-pulmonary arterial hypertension assessment and recognition of outcomes in scleroderma (PHAROS) registry. *Semin Arthritis Rheum*. 2016;45:309–14, <http://dx.doi.org/10.1016/j.semarthrit.2015.06.011>.
 96. Juge PA, Lee JS, Lau J, Kawano-Dourado L, Serrano JR, Sebastiani M, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J*. 2021;57:1–9, <http://dx.doi.org/10.1183/13993003.00337-2020>.
 97. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part I). *Chest*. 1988;93:1067–75, <http://dx.doi.org/10.1378/chest.93.5.1067>.
 98. Fischer A, Swigris JJ, Groshong SD, Cool CD, Sahin H, Lynch DA, et al. Clinically significant interstitial lung disease in limited scleroderma: histopathology, clinical features, and survival. *Chest*. 2008;134:601–5, <http://dx.doi.org/10.1378/chest.08-0053>.
 99. Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, Clements PJ, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest*. 2008;134:358–67, <http://dx.doi.org/10.1378/chest.07-2444>.
 100. Schoenfeld SR, Castellino FV. Interstitial lung disease in scleroderma. *Rheum Dis Clin North Am*. 2015;41:237–48, <http://dx.doi.org/10.1016/j.rdc.2014.12.005>.
 101. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Antoniou KM, Bissell BD, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2022;205:E18–47.
 102. Varone F, Sgalla G, Iovene B, Richeldi L. Progressive fibrosing interstitial lung disease a proposed integrated algorithm for management. *Ann Am Thorac Soc*. 2020;17:1199–203, <http://dx.doi.org/10.1513/AnnalsATS.202003-214PS>.
 103. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med*. 2002;165:1581–6, <http://dx.doi.org/10.1164/rccm.2106012>.
 104. Giménez-Palleiro A, Mazzini SP, Franquet T. Basic HRCT patterns in diffuse interstitial lung disease. *Radiologia*. 2022;64:215–26, <http://dx.doi.org/10.1016/j.rx.2022.10.003>.
 105. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol*. 2020;2:e71–83.
 106. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. *Rheumatol (United Kingdom)*. 2013;52:155–60, <http://dx.doi.org/10.1093/rheumatology/kes289>.
 107. Gilson M, Zerkak D, Wipff J, Dusser D, Dinh-Xuan AT, Abitbol V, et al. Prognostic factors for lung function in systemic sclerosis: Prospective study of 105 cases. *Eur Respir J*. 2010;35:112–7, <http://dx.doi.org/10.1183/09031936.00060209>.
 108. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N. Correlation of delta high-resolution computed tomography (HRCT) score with delta clinical variables in early systemic sclerosis (SSc) patients. *Quant Imaging Med Surg*. 2016;6:381–90, <http://dx.doi.org/10.21037/qims.2016.08.08>.
 109. Forestier A, Le Gouellec N, Béhal H, Kramer G, Perez T, Sobanski V, et al. Evolution of high-resolution CT-scan in systemic sclerosis-associated interstitial lung disease: description and prognosis factors. *Semin Arthritis Rheum*. 2020;50:1406–13, <http://dx.doi.org/10.1016/j.semarthrit.2020.02.015>.
 110. Chen A, Karwoski RA, Gierada DS, Bartholmai BJ, Koo CW. Quantitative CT analysis of diffuse lung disease. *Radiographics*. 2020;40:28–43, <http://dx.doi.org/10.1148/rg.2020190099>.
 111. Ferrazza AM, Gigante A, Gasperini ML, Ammendola RM, Paone G, Carbone I, et al. Assessment of interstitial lung disease in systemic sclerosis using the quantitative CT algorithm CALIPER. *Clin Rheumatol*. 2020;39:1537–42, <http://dx.doi.org/10.1007/s10067-020-04938-3>.
 112. Antoniou KM, Margaritopoulos GA, Goh NS, Karagiannis K, Desai SR, Nicholson AG, et al. Combined pulmonary fibrosis and emphysema in scleroderma-related lung disease has a major confounding effect on lung physiology and screening for pulmonary hypertension. *Arthritis Rheumatol*. 2016;68:1004–12, <http://dx.doi.org/10.1002/art.39528>.
 113. Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, et al. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. *Arthritis Rheumatol*. 2011;63:295–304, <http://dx.doi.org/10.1002/art.30077>.
 114. Volkman ER. Natural history of systemic sclerosis-related interstitial lung disease: how to identify a progressive fibrosing phenotype. *J Scleroderma Relat Disord*. 2019, <http://dx.doi.org/10.1177/2397198319889549>.
 115. Cottin V, Brown K. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). *Respir Res*. 2019;20, <http://dx.doi.org/10.1186/s12931-019-0980-7>.
 116. Dobrota R, Mihai C, Distler O. Personalized medicine in systemic sclerosis: facts and promises. *Curr Rheumatol Rep*. 2014;16, <http://dx.doi.org/10.1007/s11926-014-0425-8>.
 117. Hoffmann-Vold AM, Molberg Ø. Detection, screening, and classification of interstitial lung disease in patients with systemic sclerosis. *Curr Opin Rheumatol*. 2020;32:497–504, <http://dx.doi.org/10.1097/BOR.0000000000000741>.
 118. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end stage lung disease in a cohort of patients with scleroderma. *Ann Rheum Dis*. 2003;62:146–50, <http://dx.doi.org/10.1136/ard.62.2.146>.
 119. Assassi S, Leyva AL, Mayes MD, Sharif R, Nair DK, Fischbach M, et al. Predictors of fatigue severity in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. *Arthritis Res Ther*. 2010;6:R166, <http://dx.doi.org/10.1371/journal.pone.0026061>.
 120. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary

- complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol.* 2014;66:1625–35, <http://dx.doi.org/10.1002/art.38390>.
121. Volkkman ER, Tashkin DPP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. *Ann Rheum Dis.* 2019;178:122–30, <http://dx.doi.org/10.1136/annrheumdis-2018-213708>.
 122. Kanna D, Mittoo S, Aggarwal R, Proudman SM. Connective tissue disease-associated interstitial lung diseases (CTD-ILD) – report from OMERACT CTD-ILD Working Group. *J Rheumatol.* 2015;42:2168–71, <http://dx.doi.org/10.3899/jrheum.141182>.
 123. Liu X, Mayes MD, Pedroza C, Draeger HT. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? *Arthritis Care Res.* 2013;65:1375–80, <http://dx.doi.org/10.1002/acr.21968>.
 124. Wu W, Jordan S, Graf N, de Oliveira Pena J, Curram J, Allanore Y, et al. Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European scleroderma trials and research (Eustar) cohort. *Ann Rheum Dis.* 2019;78:648–56, <http://dx.doi.org/10.1136/annrheumdis-2018-213455>.
 125. Fava A, Cimbro R, Wigley FM, Liu QR, Rosen A, Boin F. Frequency of circulating topoisomerase-I-specific CD4 T cells predicts presence and progression of interstitial lung disease in scleroderma. *Arthritis Res Ther.* 2016;18:1–12, <http://dx.doi.org/10.1186/s13075-016-0993-2>.
 126. Sánchez-Cano D, Ortego-Centeno N, Callejas JL, Fonollosa Plá V, Ríos-Fernández R, Tolosa-Vilella C, et al. Interstitial lung disease in systemic sclerosis: data from the spanish scleroderma study group. *Rheumatol Int.* 2018;38:363–7, <http://dx.doi.org/10.1007/s00296-017-3916-x>.
 127. Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J.* 2020;55, <http://dx.doi.org/10.1183/13993003.02026-2019>.
 128. Arandia NI, Simeón-Aznar CP, del Castillo AG, Argüelles DC, Rubio-Rivas M, Martínez LT, et al. Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis. *Clin Exp Rheumatol.* 2017;35:S98–105.
 129. Sweet MP, Patti MG, Hoopes C, Hays SR, Golden JA. Gastro-oesophageal reflux and aspiration in patients with advanced lung disease. *Thorax.* 2009;64:167–73, <http://dx.doi.org/10.1136/thx.2007.082719>.
 130. Acharya S, Shukla S, Mahajan SN, Banode P, Mahure C, Mathew L. Interstitial lung disease in systemic sclerosis. *J Datta Meghe Inst Med Sci Univ.* 2013;8:57–9.
 131. Elhai M, Hoffmann-Vold AM, Avouac J, Pezet S, Cauvet A, Leblond A, et al. Performance of Candidate serum biomarkers for systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol.* 2019;71:972–82, <http://dx.doi.org/10.1002/art.40815>.
 132. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. *J Intern Med.* 2006;260:429–34, <http://dx.doi.org/10.1111/j.1365-2796.2006.01704.x>.
 133. Utsunomiya A, Oyama N, Hasegawa M. Potential biomarkers in systemic sclerosis: a literature review and update. *J Clin Med.* 2020;9:1–25, <http://dx.doi.org/10.3390/jcm9113388>.
 134. Asano Y, Ihn H, Yamane K, Yazawa N, Kubo M, Fujimoto M, et al. Clinical significance of surfactant protein D as a serum marker for evaluating pulmonary fibrosis in patients with systemic sclerosis. *Arthritis Rheumatol.* 2001;44:1363–9, [http://dx.doi.org/10.1002/1529-0131\(200106\)44:6<1363::AID-ART229>3.0.CO;2-5](http://dx.doi.org/10.1002/1529-0131(200106)44:6<1363::AID-ART229>3.0.CO;2-5).
 135. Tiev KP, Hua-Huy T, Kettaneh A, Gain M, Duong-Quy S, Tolédano C, et al. Serum CC chemokine ligand-18 predicts lung disease worsening in systemic sclerosis. *Eur Respir J.* 2011;38:1355–60, <http://dx.doi.org/10.1183/09031936.00004711>.
 136. Schupp J, Becker M, Günther J, Müller-Quernheim J, Riemekasten G, Prasse A. Serum CCL18 is predictive for lung disease progression and mortality in systemic sclerosis. *Eur Respir J.* 2014;43:1530–2, <http://dx.doi.org/10.1183/09031936.00131713>.
 137. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* 2017;69:1670–8, <http://dx.doi.org/10.1002/art.40130>.
 138. Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airó P, Ananieva LP, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis.* 2021;80:219–27, <http://dx.doi.org/10.1136/annrheumdis-2020-217455>.
 139. Vonk MC, Walker UA, Volkmann ER, Kreuter M, Johnson SR, Allanore Y. Natural variability in the disease course of SSC-ILD: implications for treatment. *Eur Respir Rev.* 2021;30, <http://dx.doi.org/10.1183/16000617.0340-2020>.
 140. Wu W, Jordan S, Becker MO, Dobrota R, Maurer B, Fretheim H, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. *Ann Rheum Dis.* 2018;77:1326–32, <http://dx.doi.org/10.1136/annrheumdis-2018-213201>.
 141. Morisset J, Vittinghoff E, Elicker BM, Hu X, Le S, Ryu JH, et al. Mortality risk prediction in scleroderma-related interstitial lung disease: the SADL model. *Chest.* 2017;152:999–1007, <http://dx.doi.org/10.1016/j.chest.2017.06.009>.
 142. Cottin V, Valenzuela C. Progressive pulmonary fibrosis: all roads lead to Rome (but not all at the same speed). *Eur Respir J.* 2022;60, <http://dx.doi.org/10.1183/13993003.01449-2022>.