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REVIEW

Systemic Sclerosis-Associated Interstitial Lung Disease: Improved Understanding and Advances in Management

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Abstract

Interstitial lung disease (ILD), a common manifestation of systemic sclerosis (SSc), has the highest organ-specific morbidity and mortality, particularly in patients with diffuse cutaneous SSc (dcSSc). Recent advances in diagnostics—including artificial intelligence (AI)-enhanced high-resolution computed tomography (HRCT) and biomarkers such as Krebs van den Lungen (KL)-6—have enabled earlier detection and monitoring of disease progression. Therapeutically, the approval of antifibrotics like nintedanib (NINT) and immunomodulators such as tocilizumab (Toci) has significantly expanded treatment options. Updated international guidelines from the American College of Rheumatology (ACR), American College of Chest Physicians (CHEST), American Thoracic Society (ATS), and European league against Rheumatism (EULAR) now reflect this evolving landscape. This review aims to provide a comprehensive synthesis of screening, monitoring, and therapeutic strategies in systemic sclerosis-associated interstitial lung disease (SSc-ILD), emphasizing recent advances in AI-based imaging, serological biomarkers, and updated international treatment guidelines. We conclude by highlighting the shift toward combination and potentially triple therapy approaches, and we propose future research directions aimed at improving biomarker validation, mechanistic understanding, and personalized treatment strategies.

Key words: systemic sclerosis; interstitial lung disease; screening; monitoring; management

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Introduction

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterized by fibrosis of the skin and visceral organs, as well as vasculopathy such as Raynaud's phenomenon. Pathophysiology involves factors like environmental triggers, toxins, or infectious agents causing molecular and cellular changes in genetically predisposed individuals. This leads to fibroblasts in the vessel wall and surrounding tissues transforming into myofibroblasts, which deposit increased extracellular matrix and result in vascular remodeling (Bukiri and Volkmann, 2022; Jimenez and Derk, 2004).

In the lungs, endothelial injury and immune activation drive the progression to interstitial lung disease (ILD). Antibodies targeting endothelial cells and platelet-derived growth factor receptor (PDGFR) have been implicated in disease initiation.

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Profibrotic cytokines such as transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and endothelin-1 promote fibroblast-to-myofibroblast differentiation and collagen deposition, leading to irreversible interstitial fibrosis.

Systemic sclerosis has several organ complications, including ILD. ILD occurs in up to 40% of patients with diffuse cutaneous SSc (dcSSc) and 20% of those with limited cutaneous SSc (lcSSc). The case involves repetitive injury to the pulmonary vascular tree in genetically susceptible individuals, often due to environmental factors like organic solvent or silica exposure, infections, and other oxidative stress sources. This leads to endothelial cell injury and a cascade of cellular activation, cytokine, and growth factor upregulation, resulting in interstitial inflammation and fibrosis (Allanore et al, 2015; Liakouli et al, 2024; Nihtyanova et al, 2014).

Diagnosing ILD is challenging because early symptoms are often subtle or absent. Pulmonary function tests can fail to detect up to 50% of early ILD cases. Computed tomography excels at early disease detection but comes with significant radiation exposure. New screening methods like ultrasonography, positron emission tomography (PET) computed tomography (CT), and artificial intelligence (AI)-driven high-resolution computed tomography (HRCT) analysis are being developed. Serological biomarkers looking promising for tracking disease progression may soon play a role in patient follow-up. Synthesizing each systemic sclerosis-associated interstitial lung disease (SSc-ILD) case now involves multiple parameters, that helps improve individualized understanding and management.

Pharmacotherapy has relied on off-label immunotherapies, the approval of nintenatib and tocilizumab (Toci), along with strong data on rituximab (RTX), has transformed our therapy approach. Treatment guidelines and recommendations have recently been published by the American College of Rheumatology (ACR), the American Thoracic Society (ATS) and the European league against Rheumatism (EULAR) and earlier combination therapy, especially in progressing patients may become a new treatment paradigm.

In clinical practice, the choice of therapy must be individualized based on disease phenotype and progression. Patients with predominantly inflammatory features and elevated C-reactive protein (CRP) may benefit from early initiation of tocilizumab, whereas those with fibrotic-predominant HRCT patterns may be better suited for antifibrotic therapy such as nintedanib (NINT). Rituximab can be considered in overlap syndromes or steroid-dependent disease. Combination or sequential therapy approaches are increasingly favored, particularly in progressive cases where monotherapy alone may be insufficient.

Each offers distinct frameworks for treatment initiation and escalation, with EULAR notably supporting earlier combination therapy in progressive ILD. These evolving recommendations emphasize the need for phenotype-based, individualized decision-making, and combination strategies may soon become a standard paradigm in SSc-ILD management.

This review aims to equip hospital practitioners with the essentials of SSc-ILD, covering its pathophysiology, epidemiology, and classification, along with guidance on screening, monitoring, and managing patients. Lastly the recent published

treatment guidelines are reviewed and the differences in recommendations are highlighted.

Epidemiology

SSc-ILD is more common in patients with dcSSc, Afro-American or Afro-Caribbean individuals, and males. Higher risk is also associated with anti-topoisomerase I (Scl-70) autoantibody positivity and consistently elevated CRP levels (Elhai et al, 2022; Guler et al, 2023; Nihtyanova et al, 2014). The prevalence of SSc-ILD varies globally, likely due to regional differences in SSc subtypes. In Western Europe, 44% of SSc patients have SSc-ILD, while in the Americas, the prevalence is 52.1% (Lescoat et al, 2022). The 2010 EUSTAR database showed that 19% of deaths among SSc patients were due to ILD. Pulmonary predictors of lower survival included a diffusing lung capacity for carbon monoxide (DLCO) below 40%, a forced vital capacity (FVC) below 80%, and dyspnea (Tyndall et al, 2010). Seven years later, lung fibrosis was the leading cause of death in both the general population of the database and dcSSc patients (Elhai et al, 2017).

Classification

General

SSc-ILD is identified as a chronic autoimmune-related form of ILD. 58% of patients experienced a pattern of slowly progressive lung decline over five years, whereas only 8% of patients exhibited rapid, continuously declining FVC (Hoffmann-Vold et al, 2021).

Radiographically

Radiographically, SSc-ILD is identified based on various computed tomography (CT) patterns. Non-specific interstitial pneumonia (NSIP) is observed in approximately 70–80% of cases and features ground glass opacities with traction bronchiectasis, typically showing peri-bronchial predominance (Fig. 1). At the tissue level, there is diffuse thickening of the alveolar walls with fibrosis and preservation of the alveolar architecture. The second most common radiographic pattern is usual interstitial pneumonia (UIP), which is characterized by honeycombing with or without peripheral traction bronchiectasis in a subpleural and basal predominant distribution (Fig. 2). There is significant fibrosis at the tissue level, causing distortion of the alveoli with patchy involvement alongside areas of normal lung tissue (Wijsenbeek et al, 2022). Less comhmon radiographic patterns include lymphoid interstitial pneumonia (LIP) (Fig. 3), often seen in Sjogren's syndrome; pleuroparenchymal fibroelastosis (PPFE) (Fig. 4), with fibrosis of the upper lobe pleura and adjacent parenchyma; combined pulmonary fibrosis and emphysema (CPFE) (Fig. 5), which has the highest morbidity and mortality; and organizing pneumonia (OP).

Centrilobular fibrosis (CLF) is another pattern of ILD observed in patients with SSc and is associated with gastroesophageal reflux disease (GERD). CLF can exist alone or alongside other ILD patterns previously mentioned. Radiographic charac-

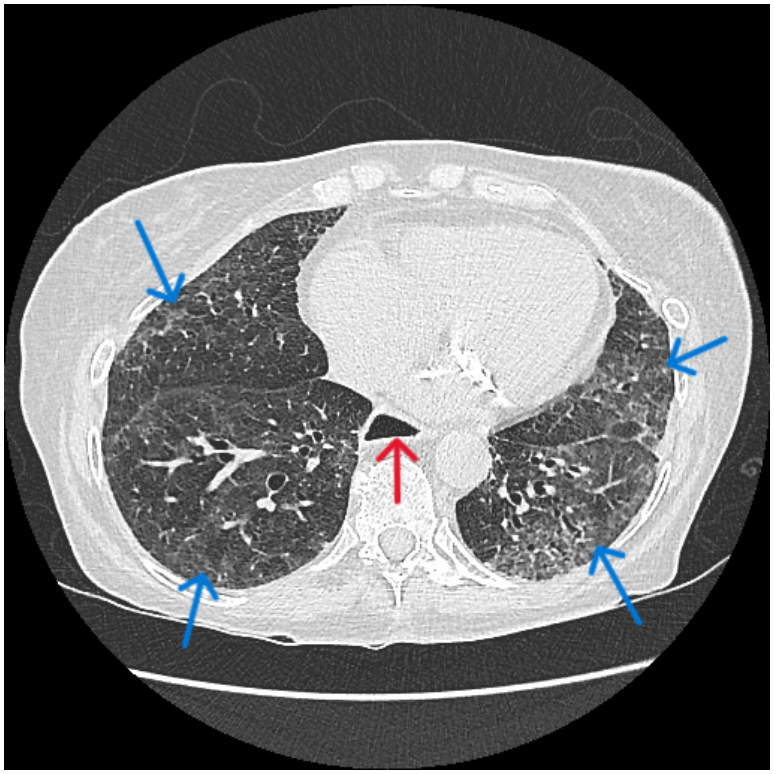

Fig. 1. SSc-NSIP. SSc-NSIP with ground glass changes (blue arrows) in a four corners pattern and patulous esophagus (red arrow). SSc, systemic sclerosis; NSIP, non-specific interstitial pneumonia.

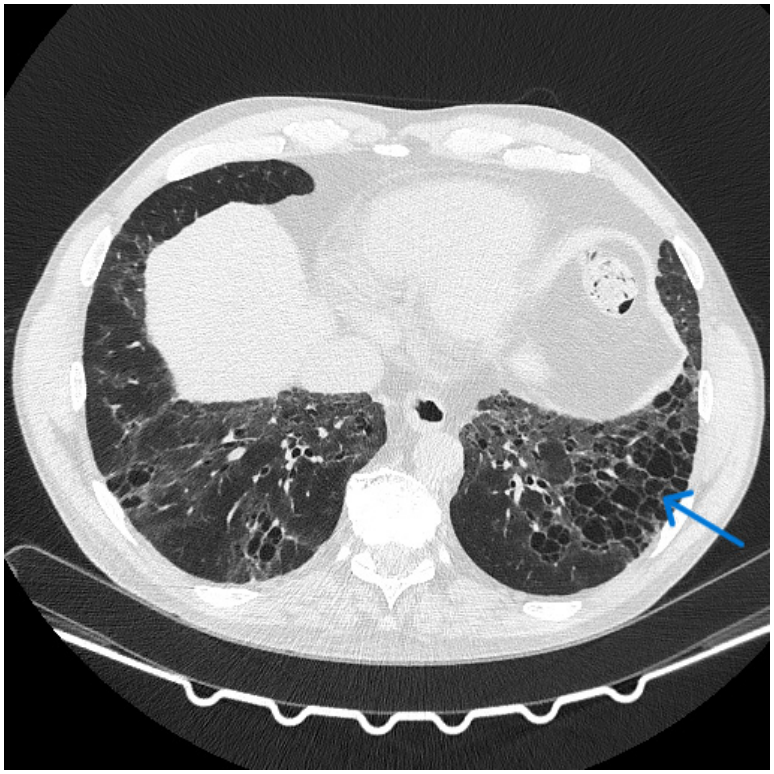

Fig. 2. SSc-UIP. SSc-UIP pattern with honeycombing changes (blue arrow). UIP, usual interstitial pneumonia.

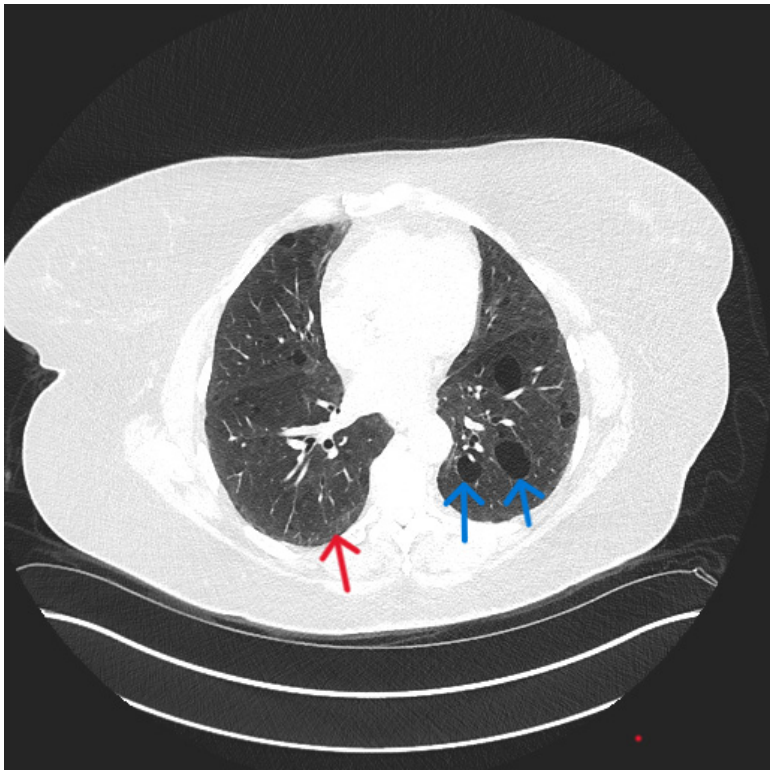

Fig. 3. SSc-LIP. SSc-LIP pattern with ground glass changes (red arrow) and thin walled cystic changes (blue arrows). LIP, lymphoid interstitial pneumonia.

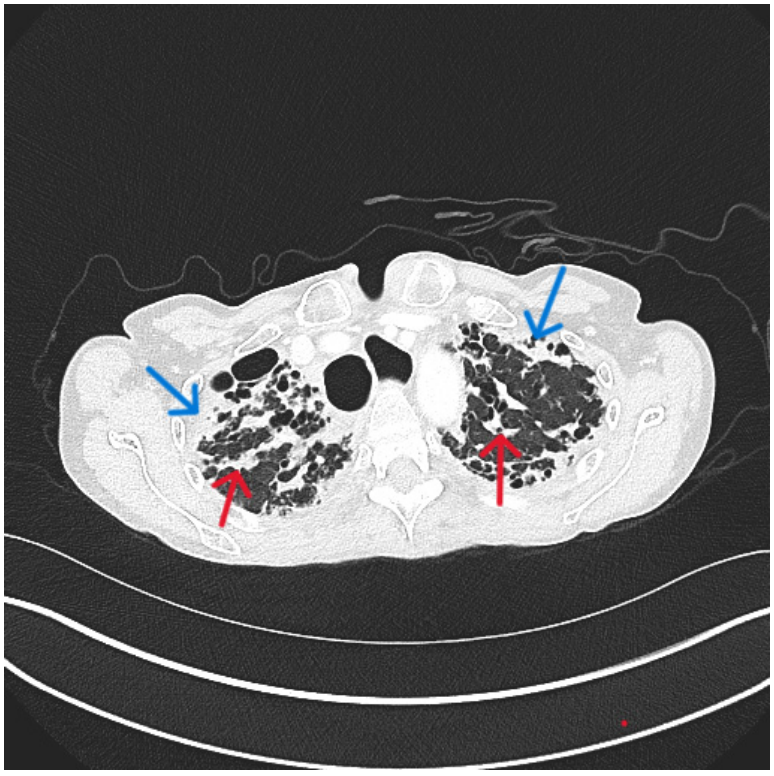

Fig. 4. SSc-PPFE. SSc-PPFE pattern with bi-apical pleural thickening (blue arrows) and pleuroparenchymal thickening (red arrows). PPFE, pleuroparenchymal fibroelastosis.

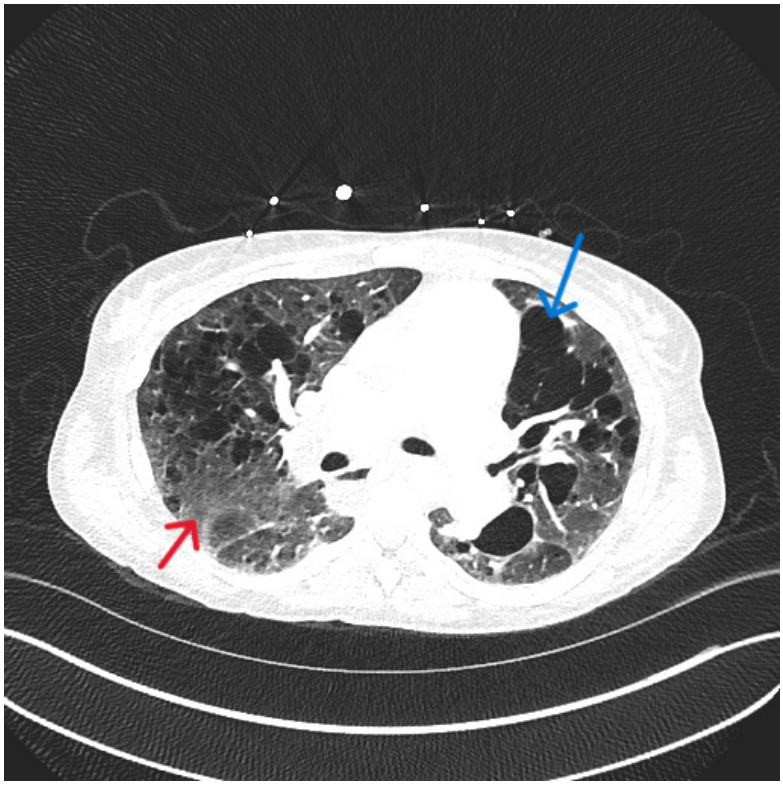

Fig. 5. SSc-CPFE. SSc-CPFE pattern with emphysema (blue arrow) and pulmonary fibrosis (red arrow). CPFE, combined pulmonary fibrosis and emphysema.

teristics include fibrosis around the small airways and interstitial fibrosis extending from the airways (Fig. 6) (Savarino et al, 2009). Managing this pattern of SSc-ILD requires a different approach, with GERD management being crucial.

Extent of Disease

Limited disease is diagnosed when less than 10% of the lungs are affected on HRCT and FVC is above 70%. Extensive disease involves more than 30% on HRCT or 10–30% with FVC below 70%, predicting higher mortality (Rackow et al, 2020).

Pathophysiology

Genetically predisposed patients with polymorphisms related to human leukocyte antigen (HLA), interferon pathway, immunity, and cell death may lose self-tolerance and produce autoantibodies against vascular molecules when exposed to oxidative stress, viral infections, silica, or organic solvents. Researchers have found antibodies targeting endothelial cells in patients with SSc-ILD, although their harmful effect is unconfirmed. Endothelial cell activation triggers coagulation, especially thrombin activation, early in lung disease, and produces endothelin-1, which stimulates fibroblasts. This leads to a prothrombotic environment, B and T cell activation, and an increase in cytokine and profibrotic growth factors that lead to transdifferentiating lung fibroblasts to lung myofibroblasts (Liakouli et al, 2024). Early inflammation in the alveoli is indicated by increased cellularity in the bronchoalve-

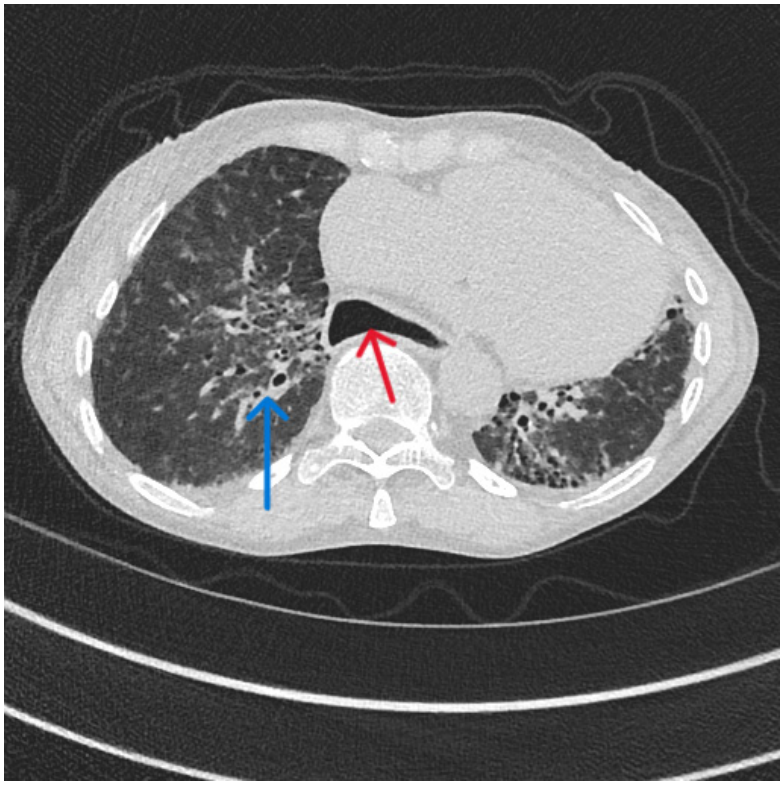

Fig. 6. SSc-CLF. SSc-CLF pattern with peri-brochial fibrosis (blue arrow) and patulous esophagus (red arrow). CLF, centrilobular fibrosis.

olar lavage fluid, with higher percentages of neutrophils and eosinophils, and sometimes a lower cluster of differentiation ($CD4^+/CD8^+$) ratio. Antibodies targeting the platelet derived growth factor receptor (PDGFR) may cause fibroblasts to produce oxygen-free radicals and collagen, in turn also helping in transforming them into myofibroblasts. The interaction between triggers, autoimmunity, inflammation, genetic and epigenetic predisposition in SSc-ILD is still not well understood (Liakouli et al, 2024; Renzoni et al, 2021; Reyfman et al, 2019; Ryu et al, 2020).

Risk Factors for ILD in SSc

Up to 42% of dcSSc patients develop ILD, compared to around 22% of lcSSc patients, making ILD more likely in those with extensive skin involvement. Male patients and those of Afro-American or Afro-Caribbean descent are at higher risk. Patients with low baseline FVC and DLCO, elevated CRP levels, or having the anti-Scl-70 antibody also have a higher likelihood of developing ILD. Exposure to crystalline silica and solvents like trichloroethylene further increases the risk of SSc-ILD (Elhai et al, 2022; Guler et al, 2023; Nihtyanova et al, 2014).

Clinical

Presentation

Initial symptoms may include mild dyspnea on exertion, decreased exercise capacity, and a dry chronic cough. Early auscultatory findings, such as basal crackles, might be absent, and up to 50% of patients with early signs of ILD on chest CT can have normal pulmonary function tests (PFTs). The most sensitive and specific method to diagnose SSc-ILD is by HRCT, which should be performed in all SSc patients at initial diagnosis as a baseline (Hoffmann-Vold et al, 2019).

Screening

Every SSc patient should undergo a thorough physical exam, including pulmonary and cardiac evaluations. Initially, all should have HRCT and PFTs, with PFTs repeated every 6–12 months if normal or more frequently if abnormal. Progressive SSc-ILD patients will continue to decline regardless of therapy, which only slows the rate of decline. Continual monitoring is crucial for patients, especially those with active progression (Distler et al, 2025). Advances in radiographic screening are being explored in SSc-ILD. A study using Quantitative fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET-CT on 15 patients showed it could detect early severe dcSSc-ILD by identifying metabolic activity in the lungs, correlating with higher ILD involvement (>20% of the lung) and lower DLCO %. This tool may better identify small progression levels compared to HRCT or PFTs (Broens et al, 2024). In another study, automated artificial intelligence (AI)-based image analysis of HRCTs was used to quantify and predict ILD in SSc patients. Seventy-five patients with SSc-ILD were evaluated, and those who exhibited progressive pulmonary fibrosis (PPF) had more extensive radiographic lesions and a more pronounced decrease in FVC (Guiot et al, 2025). Lung ultrasound is a convenient option for outpatient offices, proven to correlate well with HRCT findings in SSc-ILD patients when performed by an experienced sonographer (Watanabe et al, 2024).

Bronchoalveolar lavage (BAL) is a useful tool for ruling out infections during acute lung deterioration but not for diagnosis or follow-up. Lung biopsy is neither required nor recommended for diagnosis.

Monitoring Disease Progression

Progression of SSc-ILD according to Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) criteria is defined as an FVC decline of more than 10% from baseline or an FVC decline of 5–9% from baseline paired with a DLCO decline of more than 15%. The FVC may be influenced by respiratory muscle involvement or thoracic skin restriction, while the DLCO may be affected by pulmonary vascular involvement. HRCT monitoring lacks standardization: some clinicians test yearly or biennially, while others limit cuts to reduce radiation. Detecting small short-term changes can be difficult. Studies show that a radiographic change of over 2% suggests worse prognosis. In a study of 826 patients with SSc-ILD, 58% of patients experienced a pattern of lung function decline over 5 years, whereas only 8% showed a rapid, continuously declining FVC. The strongest pre-

dictors for FVC decline were male sex, higher modified Rodnan skin score (mRSS), and reflux/dysphagia symptoms. Most patients had both progressive and stable periods, indicating that disease progression in one period may not predict subsequent progression (Hoffmann-Vold et al, 2021). As both PFTs and HRCT have their limitations in detecting small changes that suggest progression which are important to guide therapy, AI-based image analysis of HRCT and PET-CT may be the new way of monitoring SSc-ILD progression (Broens et al, 2024; Guiot et al, 2025). In addition to radiographic and clinical measures of progression, biological markers are also a hot topic in SSc-ILD and recent work using blood samples from the Scleroderma lung study II (SLS II) where mycophenolic mofetil (MMF) was compared to cyclophosphamide (CTX) in a randomized control study of SSc-ILD with progressive disease. The study was investigating multiple circulating biomarkers and if they could predict PPF in patients in the two arms of the study. Out of these markers a higher serum Krebs van den Lungen (KL)-6 factor level correlated with the development of PPF in patients in both arms of the study (Volkmann et al, 2025).

Management

Decisions

Managing patients with SSc-ILD requires considering multiple factors. Key aspects include the extent and progression of ILD, extra respiratory manifestations, patient age, comorbidities, priorities, radiographic patterns, and PFT progress. A multidisciplinary discussion is essential to make an informed decision.

Therapies

Cyclophosphamide

CTX was a standard treatment for years until less toxic options proved equally effective. It causes the cell death of dividing lymphocytes and effects both humoral and cellular immunity. A recent 2024 meta-analysis by Barnes et al (2024) found that CTX significantly improved forced vital capacity (FVC) compared to placebo, although it had higher rates of adverse effects and discontinuation than MMF. These findings underscore CTX's clinical efficacy, while also highlighting its safety limitations (Barnes et al, 2024). Further support comes from the RECITAL trial, a 2022 multicenter, double-blind randomized controlled trial comparing intravenous CTX with rituximab in connective tissue disease-associated ILD, including patients with SSc. The study demonstrated that rituximab was not superior to CTX to treat patients with connective tissue disease (CTD)-ILD, although participants in both treatment groups had increased FVC at 24 weeks, in addition to clinically important improvements in patient-reported quality of life (Maher et al, 2023). The 2023 EULAR recommendations continue to support CTX as a conditional treatment option for SSc-ILD, especially in patients with progressive disease who may not be candidates for alternative agents (Del Galdo et al, 2025).

Mycophenolate Mofetil

The SLS II was designed as a superiority study comparing MMF vs CTX for patients with SSc-ILD with Raynaud's symptoms <7 years and FVC between 45

and 85%. Seventy-three patients were randomized to oral CTX at 2 mg/kg/day for 1 year and then 1 year of placebo, while sixty-nine patients in the MMF group received 3 grams per day for 2 years. The primary outcome was the FVC % predicted over time from 3 months to 24 months. At 24 months the FVC improved both in the CTX and MMF group though the MMF group had fewer premature withdrawals and less frequent leukopenia and thrombocytopenia (Tashkin et al, 2016). While this study did not allow for its approval it catapulted MMF to be the preferred first line therapy for SSc-ILD even in the most recent society guidelines. It is well tolerated and it is typically titrated up to 3 gr/day.

Rituximab

The DESIRES study compared rituximab (RTX) vs placebo in SSc patients with a modified Rodnan skin score (mRSS) >10. Patients were randomized to RTX 375 mg/m^2 intravenous (IV) every week for 4 weeks or placebo with the primary outcome being the mRSS at 24 weeks while secondary outcomes included the FVC. The skin score showed improvement while the FVC showed stabilization in the RTX as compared to a decline in the placebo arm at 24 weeks (Ebata et al, 2021).

In the RECITAL study RTX vs CTX was compared in progressive ILD in SSc (n = 37), inflammatory myositis and mixed connective tissue disease. The primary outcome measure was the rate of change of FVC at 24 weeks both groups had equivalent improvement in the FVC (Maher et al, 2023).

The EVER-ILD study looked at RTX in combination with MMF vs placebo with MMF in patients with NSIP out of which twenty-three were SSc-ILD. At 6 months the combination therapy showed better results in the change of FVC % (Mankikian et al, 2023). A recent meta-analysis concluded that RTX use in SSc-ILD can stabilize lung function though additional research is needed (Macrea et al, 2024). Rituximab can be used both as mono- or combination therapy specifically with MMF to manage patients with SSc-ILD. Often SSc and non-SSc comorbidities, lack of efficacy of other agents, and patient specific characteristics drive the clinician's decision as to the use of RTX.

Tocilizumab

The FaSScinate trial looked at tocilizumab (Toci) vs placebo in patients with dcSSc +/- ILD with disease less than 5 years and mRSS between 15 and 40 and a CRP more than 10. The FVC % at both 24 and 48 weeks showed less worsening in the tocilizumab group (Khanna et al, 2016). The FocuSSced looked at Toci vs placebo in dcSSc +/- ILD with disease of less than 60 months, mRSS between 10–35 and CRP more than 10. The FVC at 48 weeks was a secondary outcome with the mRSS being the primary outcome measure. At 48 weeks the difference in the mRSS was no different between the two groups but the FVC showed significance, and this led to the Food and Drug Administration (FDA) approval of Tocilizumab for SSc-ILD (Khanna et al, 2020). Since its approval, Toci is used as mono- or combination therapy, often with MMF and less frequently with RTX, and sometimes in combination with nintedanib (NINT). The studies referenced were conducted

in SSc-ILD patients who had an inflammatory type of disease. As a result, clinicians tend to use this agent when their patients have a persistently elevated CRP or concomitant arthritis.

Nintedanib

The largest treatment trial for SSc-ILD looked at NINT vs placebo in patients who on HRCT had lung involvement of more than 10% and a FVC above 40%. Out of the population enrolled 48% were on mycophenolate mofetil. Two hundred and eighty-eight patients were randomized to NINT and another group of the same size were in the placebo group. The primary measure, the rate of decline of the FVC % at 52 weeks was significantly better in the NINT group and in 2019 NINT was approved for SSc-ILD (Distler et al, 2019). It functions as an anti-fibrotic agent and is often favored in patients who have more fibrotic lung disease on their HRCT. Typically used in combination with MMF or Toci, the combination works both on the inflammatory and fibrotic aspect of the disease. It is limited by the significant GI side effects which are seen in the majority of patients.

Other Agents

In the STRATUS trial abituzumab vs placebo was looked at for SSc-ILD, though the study was terminated due to slow enrollment (Khanna et al, 2021). In Scleroderma Lung Study (SLS) III pirfenidone was to be looked at for SSc-ILD. It was designed to supplement the SLS I and II studies which have helped solidify the standard of care for SSc-ILD. Unfortunately, the study had to prematurely stop recruitment due to the COVID-19 pandemic.

Practical Considerations for Treatment Selection

Therapy selection in SSc-ILD must be individualized based on clinical phenotype, disease trajectory, and comorbidities. For instance, MMF remains the preferred first-line agent in most cases given its tolerability and long-term efficacy data. Tocilizumab is often used in patients with systemic inflammation, while nintedanib is indicated for fibrotic-predominant ILD with evidence of progression. Rituximab may be favored in patients with overlap features or refractory symptoms. In more severe or rapidly deteriorating disease, short-course CTX may be used for induction, followed by maintenance with MMF. Real-world clinical judgment often requires flexible sequencing or combination approaches tailored to the patient's evolving phenotype.

Hematopoietic Stem Cell Autograft

Three randomized control studies looked at autologous hematopoietic stem cell transplants (AHSCT) with high dose CTX followed by bone marrow autograft in patients with a recent diagnosis of SSc. Patients improved their medium-term prognosis but had early increased mortality. In one of these studies, the ASTIS trial at 2 years the FVC improved in the autograft but declined in the control group (Burt et al, 2011; Sullivan et al, 2018; Van Laar et al, 2014). The use of AHSCT has often been as a last resort therapy because of early increased morbidity and mortality, as well as high cost and a requirement for significant patient commitment.

Who Should Be Treated?

Patients who have progressive lung disease, with an FVC <80% and any degree of ILD or symptoms; patients with 20% of lung involvement on HRCT or patients with more than 10% lung involvement with abnormal pulmonary function tests; patients at high risk for ILD progression such as early dcSSc, anti-Scl-70 positive; though even patients with evidence of mild ILD, less than 10% should also be considered; as well as patients with worsening HRCT with symptoms of declining pulmonary function tests; and patients with exertional desaturation on SpO_2 (Rahaghi et al, 2023).

Recent Treatment Guidelines

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guidelines for the Treatment of ILD in Systemic Autoimmune Rheumatic Diseases (SARD)

In 2023 the ACR/CHEST presented recommendations for the management of SARD-ILD, and specifically recommendations for SSc-ILD. They achieved this based on systematic reviews of the available data for each individual therapy, and these recommendations which came from these reviews were then voted on by an expert voting panel of rheumatologists, pulmonologist, a radiologist and patients to be given a final score and recommendation. The conditional first line therapy based on these guidelines were MMF, Toci and RTX, while in the additional options, CTX, NINT and azathioprine are also listed. A strong recommendation against using glucocorticoids (GCs) was suggested in these guidelines. The guidelines further suggest that if there is progression of ILD on first-line therapy adding or switching therapy is recommended and the conditional preferred therapies are MMF, RTX, NINT, Toci, CTX and AHSCT, while GCs can be used for short term bridging between therapies though strongly recommend against long term use. The guidelines also make a strong point that all therapies are conditional and shared decision-making with pulmonary is recommended (Johnson et al, 2024).

American Thoracic Society (ATS) Guidelines for the Treatment of SSc-ILD

In 2024 the ATS published its own clinical practice guidelines which were focused on the use of separate therapies on their own or in combination for SSc-ILD. They achieved this by doing individual systematic reviews to analyze the available data for each therapeutic option. The committee consisted of rheumatologists, pulmonologists and patients who voted on deciding on the strength of the individual guideline based on the available evidence. The committee refrained from creating a treatment algorithm as they believed there is a lack of strong data to do so, as is also the recommendations of specific combination therapies. They gave a strong recommendation for MMF and conditional in favor of CTX, RTX, Toci, NINT and combination MMF and NINT (Raghu et al, 2024).

EULAR Recommendations for the Treatment of Systemic Sclerosis:2023 Update

In 2023 EULAR updated its treatment guidelines for the treatment of SSc as well as specific treatment guidelines for SSc-ILD. The process they undertook in these cases was to have active EULAR centers to propose treatment questions for

SSc. A systematic literature review regarding the treatment questions took place and the task force by voting decided to maintain the previously published guidelines or make changes to those guidelines. The guidelines suggested that MMF, RTX or CTX should be considered for the treatment of SSc-ILD, NINT should be considered alone or in combination with MMF, and Toci should also be considered for the treatment of SSc-ILD and specifically in early inflammatory patients (Del Galdo et al, 2025) (Fig. 7).

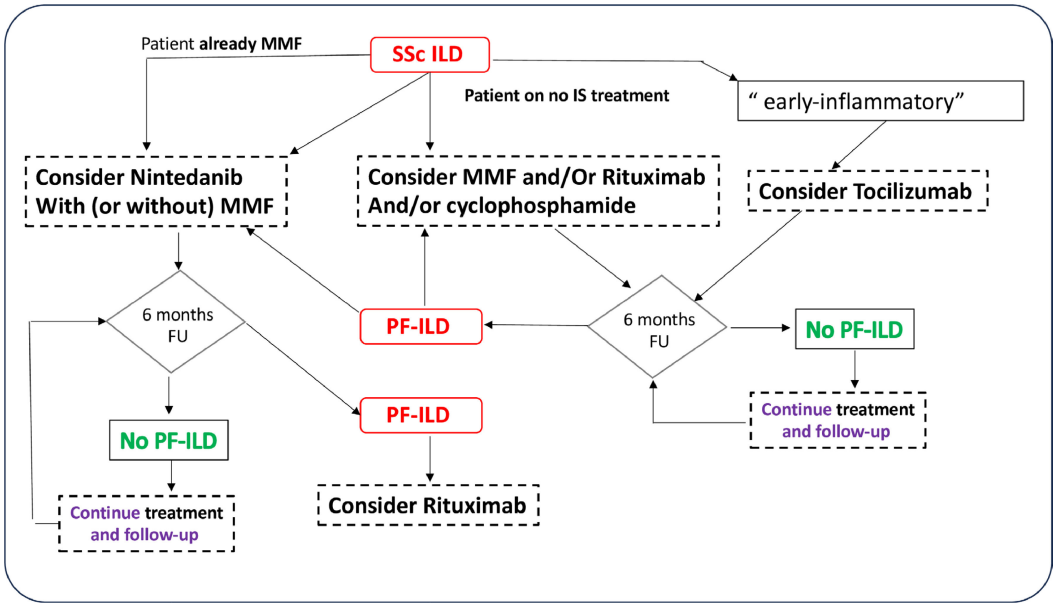

Fig. 7. EULAR recommendations for the treatment of SSc-ILD. Reprinted from (Del Galdo et al, 2025), available under the CC BY-NC-ND license (http://creativecommons.org/licenses/bync-nd/4.0/). EULAR, European league against Rheumatism; MMF, mycophenolic mofetil; IS, immune suppressive; FU, follow-up; ILD, interstitial lung disease; PF, pulmonary fibrosis.

Though all major societies agree on the importance of early recognition and immunosuppression, their guidance diverges in structure and emphasis. ACR/CHEST proposes a tiered, severity-based escalation model, while ATS recommendations focus on agent-specific data without a formal algorithm. EULAR's recent update notably endorses earlier use of combination therapy in progressive phenotypes, reflecting an evolving approach to treatment intensification. These differences can influence therapeutic decision-making across practice settings and highlight the need for more standardized clinical pathways. In reality, clinicians often default to individualized sequencing or combination therapy based on disease trajectory—sometimes outpacing the caution reflected in current guideline structure.

Adjunctive Measures to Improve Outcomes

Important to the management of SSc-ILD is not only therapy directed to this but also managing other aspects of SSc which could affect pulmonary symptoms. Intense GERD relates to worse PFTs in SSc and degree of pulmonary fibrosis thus treatment of GERD is highly recommended, but also recommendations to avoid silent micro aspiration which is deemed to be causative of SSc-ILD progression in

some cases. Tobacco use needs to be curtailed, and pulmonary rehab needs to be part of the general management of these patients. Vaccinations for respiratory illnesses should be strongly recommended and when needed oxygen supplementation should be provided (Katz et al, 2022; Savarino et al, 2009).

Lung Transplantation

In carefully selected SSc-ILD patients who have not responded to therapy and have no contraindications, lung transplantation needs to be considered. While in the past the concern of micro aspiration made SSc patients poor candidates, the advancement in management and the use of enteral feedings post-transplant has made SSc patients more favorable candidates to the transplant teams. Overall survival after lung transplantation in SSc-ILD is comparable to other indications especially in institutions that have strong experience in doing this, with a 1-year survival of 80.6% (Minalyan et al, 2021).

Conclusion

Interstitial lung disease remains the most serious pulmonary manifestation of systemic sclerosis, particularly in dcSSc. Although early symptoms may be subtle, timely diagnosis is now achievable with advanced imaging, AI-based quantification, and biomarker tracking. Serum biomarkers are also a hot topic in SSc-ILD especially regarding identifying progression and KL-6 appears to be the most promising and is already available for clinical use through specialty-based laboratories.

Treatment has progressed beyond empirical immunosuppression to include targeted biologics and antifibrotics, guided by updated recommendations from ACR/CHEST, ATS, and EULAR. These guidelines emphasize mycophenolate mofetil as a first-line agent, with conditional roles for rituximab, tocilizumab, Nintedanib, and short-term CTX.

Crucially, treatment strategy is shifting toward additive approaches that address both inflammatory and fibrotic pathways. Combination and potentially triple therapy regimens may become the norm, though robust data are still lacking. Future research must prioritize prospective validation of biomarkers, AI diagnostic tools, and comparative trials of combination regimens.

As treatment algorithms evolve, the role of combination and phenotype-driven therapy will become increasingly central. Future strategies may incorporate biomarker profiles, AI-quantified HRCT progression, and functional decline thresholds to guide escalation. These tools can help clinicians move beyond trial-based generalizations and toward precision medicine models that better reflect the heterogeneity of SSc-ILD in practice. Shared decision-making, multidisciplinary collaboration, and personalized care will be essential to improving outcomes in this complex disease.

Future Directions

• Investigate combination and triple therapy regimens targeting both inflammation (e.g., Toci, RTX) and fibrosis (e.g., NINT).

• Validate serum biomarkers (Krebs von den Lungen-6 (KL-6), chemokine ligand-18 (CCL-18), surfactant protein-D (SP-D)) and develop composite indices for progression prediction.

• Standardize AI-based HRCT quantification in routine care.

• Conduct mechanistic studies on fibroblast differentiation, autoantibody function, and immune-fibrotic signaling.

• Develop stratified treatment algorithms based on disease phenotype, progression, and serologic profile.

Key Points

- Interstitial lung disease (ILD), a common manifestation of systemic sclerosis (SSc), has the highest organ-specific morbidity and mortality, particularly in diffuse cutaneous SSc (dcSSc).
- Diagnosing SSc-ILD is challenging due to subtle or absent early symptoms, and although HRCT is effective, it carries radiation risks.
- Screening is evolving with PET-CT, ultrasound, and especially AI-based HRCT and KL-6 biomarkers, which may soon be integrated into standard algorithms.
- Current guidelines based on systematic reviews recommend MMF as first-line therapy, with conditional support for agents like RTX, CTX, Toci, and NINT.
- The field is shifting toward combination and triple therapy strategies, guided by disease phenotype and interdisciplinary collaboration.

Availability of Data and Materials

Not applicable.

Author Contributions

AS: Manuscript design, review, editing. CTD: Manuscript initial draft, design, review, editing. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The individual radiographic studies were obtained from patients. According to our institutional policy, informed consent was not required because no patient identifiers were included.

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Conflict of Interest

Chris T Derk is serving as one of the Editorial Board Members of this journal. We declare that Chris T Derk had no involvement in the review of this article and has no access to information regarding its review. The authors declare no conflict of interest.

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