# PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS: INTERSTITIAL LUNG DISEASE AND PULMONARY ARTERIAL HYPERTENSION

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**Abstract**

**Background:** Systemic sclerosis (SSc) is an immune-mediated connective tissue disease in which pulmonary involvement — chiefly interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) — is now the leading cause of disease-related mortality, having overtaken scleroderma renal crisis as management of the latter has improved.

**Methods:** This narrative review synthesizes current evidence on the pathogenesis, screening, diagnosis, and treatment of SSc-ILD and SSc-PAH, drawing on the 2023 American College of Rheumatology (ACR)/CHEST guideline on ILD screening in systemic autoimmune rheumatic disease and the 2023 EULAR recommendations for the management of systemic sclerosis.

**Results:** ILD, present in roughly two-thirds of SSc patients, arises from fibroblast activation and progressive collagen deposition and is best detected by high-resolution CT and monitored with serial pulmonary function testing. PAH, affecting up to a quarter of patients, arises from a distinct obliterative pulmonary vasculopathy and is screened for with echocardiography or the DETECT algorithm before confirmation by right heart catheterization. Because early symptoms of both conditions are non-specific and often overlap with other manifestations of SSc, structured, lifelong screening protocols are essential, since treatment delay is strongly associated with worse survival. Antifibrotic and immunosuppressive agents (mycophenolate mofetil, nintedanib, tocilizumab) are the mainstay for ILD, while endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and

prostacyclin pathway agents, increasingly used as upfront combination therapy, are the mainstay for PAH.

**Conclusion:** Because SSc-ILD and SSc-PAH are pathobiologically distinct but clinically overlapping, systematic, protocol-driven screening and mechanism-specific rather than one-size-fits-all treatment are central to reducing pulmonary mortality in systemic sclerosis, including in resource-limited settings such as Uzbekistan, where structured pulmonary function testing and echocardiographic screening remain feasible even where advanced PAH therapies are not always accessible.

**Keywords**

Systemic sclerosis, scleroderma, interstitial lung disease, pulmonary arterial hypertension, high-resolution CT, DETECT algorithm, right heart catheterization, nintedanib, endothelin receptor antagonist.

**Methods**

This work was prepared as a narrative literature review. A literature search was conducted in September 2026 using PubMed, the ACR and EULAR publication databases, and the websites of major pulmonology and rheumatology societies, with the search terms "systemic sclerosis," "scleroderma," "interstitial lung disease," "pulmonary arterial hypertension," "DETECT algorithm," and "nintedanib," combined with filters for publication in English between 2007 and 2026. Priority was given to the 2023 ACR/CHEST ILD screening guideline, the 2023 EULAR recommendations for systemic sclerosis management, randomized controlled trials of antifibrotic and PAH-targeted therapy, and prospective screening cohort studies; narrative summaries from established clinical reference sources were included for foundational background. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

**Introduction**

Systemic sclerosis is a chronic autoimmune disease characterized by widespread microvascular injury, immune dysregulation, and progressive fibrosis of the skin and internal organs. Among its visceral manifestations, pulmonary involvement carries the greatest prognostic weight: interstitial lung disease and pulmonary arterial hypertension together now account for the largest share of SSc-related deaths, having surpassed scleroderma renal crisis as outcomes for the latter improved with angiotensin-converting enzyme inhibitor therapy.

Although both conditions arise from the same underlying disease and frequently coexist in the same patient, they are pathobiologically distinct — one predominantly a fibrotic process of the lung parenchyma, the other predominantly

an obliterative vasculopathy of the pulmonary arterioles — and this distinction has direct consequences for screening strategy, diagnostic work-up, and choice of therapy. A further challenge is that early symptoms of both conditions, principally exertional dyspnoea, are non-specific and easily attributed to deconditioning, musculoskeletal disease, or other manifestations of SSc, so that structured, protocol-driven screening rather than symptom-triggered evaluation is required to detect disease before irreversible damage accrues.

*The aim of this review is to summarize the divergent pathogenesis of SSc-ILD and SSc-PAH, outline current screening and diagnostic strategies for each, and review mechanism-specific treatment approaches, with attention to their relevance to rheumatology and pulmonology practice in Uzbekistan.*

Understanding and correctly managing pulmonary involvement in systemic sclerosis is relevant across several areas of clinical practice, including:

- Rheumatology (disease subtyping, autoantibody-guided risk stratification, immunosuppressive treatment)
- Pulmonology (interpretation of HRCT and pulmonary function testing, antifibrotic therapy)
- Cardiology (echocardiographic screening, right heart catheterization, PAH-targeted therapy)
- Primary care and internal medicine (recognition of unexplained dyspnoea as a red flag)
- Radiology (HRCT pattern recognition, distinguishing NSIP from other interstitial patterns)

**Divergent Pathogenesis: One Disease, Two Pulmonary Pathways**

Both SSc-ILD and SSc-PAH originate from the same core disease process — microvascular endothelial injury combined with dysregulated immune activation and fibroblast signalling — but the two conditions diverge sharply in the pulmonary compartment they predominantly affect. In SSc-ILD, alveolar epithelial injury triggers an inflammatory infiltrate that drives myofibroblast activation and excessive extracellular matrix and collagen deposition within the lung interstitium, producing a predominantly restrictive physiological pattern with progressive loss of forced vital capacity and lung volumes. The non-specific interstitial pneumonia (NSIP) pattern is the most common histological and radiological correlate, in contrast to the usual interstitial pneumonia pattern that predominates in idiopathic pulmonary fibrosis.

In SSc-PAH, by contrast, the dominant process is a progressive obliterative vasculopathy of the small pulmonary arterioles: endothelial dysfunction promotes intimal and medial thickening, in-situ thrombosis, and eventually plexiform lesions that progressively narrow the vascular lumen, increasing pulmonary vascular

resistance and right ventricular afterload independent of any parenchymal lung disease. Because these two pathways can act independently or in combination, patients with SSc may develop isolated ILD, isolated PAH, ILD complicated by secondary (group 3) pulmonary hypertension, or true group 1 PAH superimposed on underlying fibrosis, each of which carries different prognostic and therapeutic implications. This divergence, and its shared downstream consequence of right ventricular strain, is illustrated in Figure 1.

**Figure 1. Divergent Pulmonary Pathobiology in Systemic Sclerosis**

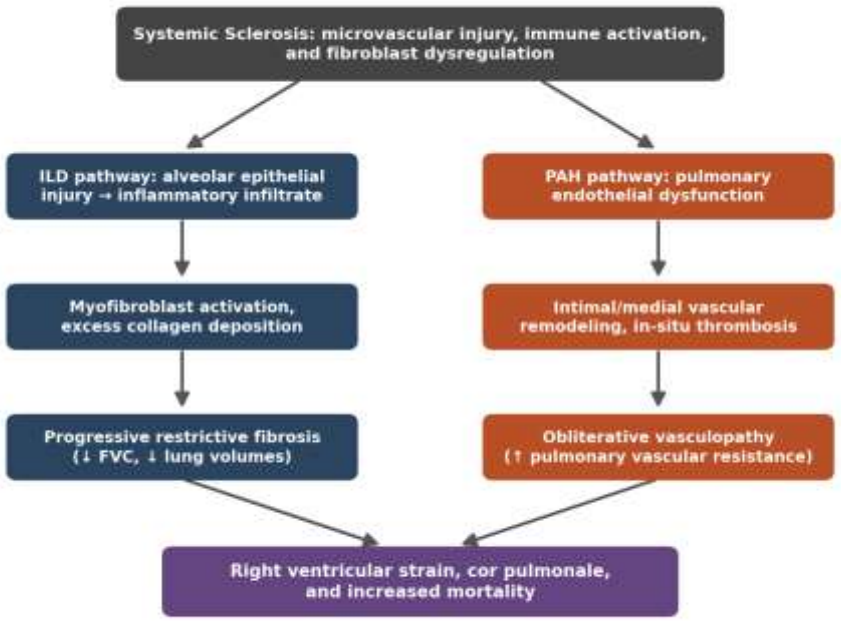


*Figure 1. Interstitial lung disease and pulmonary arterial hypertension arise from a shared systemic sclerosis substrate but follow pathobiologically distinct fibrotic and vasculopathic pathways that converge on right ventricular strain.*

**Screening and Diagnosis**

Because both conditions are frequently asymptomatic or minimally symptomatic in their early, most treatable stages, current guidelines recommend structured baseline and longitudinal screening for every patient with confirmed SSc rather than evaluation triggered only by symptoms. At the time of SSc diagnosis, baseline high-resolution CT of the chest and full pulmonary function testing with diffusing capacity for carbon monoxide (DLco) are recommended to detect ILD, while baseline transthoracic echocardiography (with or without natriuretic peptide measurement) is used to screen for PAH. Risk stratification refines the intensity of subsequent surveillance: anti-topoisomerase I (anti-Scl-70) antibodies, diffuse cutaneous disease, and a high modified Rodnan skin score identify patients at elevated risk of ILD, whereas anti-centromere antibodies,

longer disease duration, and an isolated fall in DLco out of proportion to forced vital capacity identify patients at elevated risk of PAH. These distinguishing features are summarized in Table 1.

**Table 1. Comparative Features of SSc-Associated Interstitial Lung Disease and Pulmonary Arterial Hypertension**

| Feature | Interstitial Lung Disease | Pulmonary Arterial Hypertension | Overlap |
|---|---|---|---|
| **Core mechanism** | Fibroblast activation and collagen deposition in alveolar interstitium | Endothelial dysfunction and obliterative remodeling of pulmonary arterioles | Shared vasculopathy |
| **Key risk markers** | • Anti-Scl-70 (topoisomerase I)<br>• Diffuse cutaneous subtype<br>• High modified Rodnan skin score | • Anti-centromere antibody<br>• Long disease duration<br>• Isolated low DLco (out of proportion to FVC) | Nucleolar ANA pattern |
| **Primary screening test** | High-resolution CT of the chest | Transthoracic echocardiography, DETECT algorithm | PFT with DLco |
| **Confirmatory test** | HRCT pattern (NSIP most common) plus restrictive PFT | Right heart catheterization (mPAP >20 mmHg, PVR >2 Wood units, PAWP ≤15 mmHg) | — |
| **First-line therapy** | Mycophenolate mofetil or nintedanib; tocilizumab in progressive disease | Endothelin receptor antagonist plus PDE-5 inhibitor (upfront combination) | Avoid smoking, hypoxia |

Because transthoracic echocardiography alone has limited sensitivity for early PAH and can be technically difficult to interpret in patients with coexisting ILD, composite screening tools such as the DETECT algorithm — which combines pulmonary function results, autoantibody status, electrocardiographic findings, and

serum biomarkers including NT-proBNP and urate — have been developed to improve early, non-invasive detection and to identify which patients warrant referral for right heart catheterization, the only test that definitively confirms PAH. Ongoing surveillance intervals and escalation triggers for both conditions are summarized in Table 2.

**Table 2. Recommended Screening and Monitoring Schedule for SSc-ILD and SSc-PAH**

| Time Point | ILD Assessment | PAH Assessment | Trigger to Escalate |
|---|---|---|---|
| **At SSc diagnosis (baseline)** | Baseline HRCT chest, full PFT with DLco | Baseline transthoracic echocardiogram, NT-proBNP | Any HRCT fibrosis or DLco <80% |
| **First year after ILD diagnosis** | Full PFT with DLco every 3–6 months | Ambulatory desaturation testing every 3–12 months | FVC decline ≥10% (or ≥5% with DLco decline) |
| **Annual, lifelong (all SSc patients)** | PFT with DLco; repeat HRCT if clinically indicated | DETECT algorithm or echocardiography; low threshold if unexplained dyspnea | Estimated systolic PAP elevation or isolated DLco fall |
| **Positive screen** | High-resolution CT to confirm/characterize fibrosis pattern | Right heart catheterization for definitive diagnosis | Confirmed diagnosis → start mechanism-specific therapy |

This lifelong, cyclical process of baseline assessment, risk stratification, scheduled reassessment, and confirmatory testing when screening is abnormal is summarized in Figure 2.

Figure 2. The SSc Pulmonary Screening and Monitoring Cycle

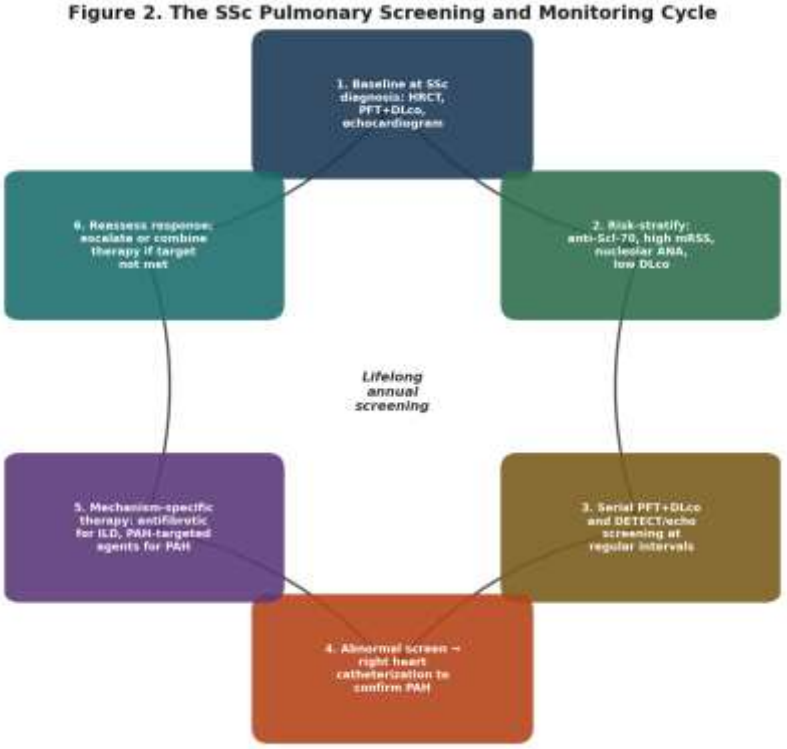


*Figure 2. The recurring pulmonary screening and monitoring cycle in systemic sclerosis: baseline testing, risk stratification, serial surveillance, confirmatory testing when screening is abnormal, mechanism-specific treatment, and reassessment.*

**Treatment: Mechanism-Specific Therapy**

As with diagnosis, treatment of SSc-ILD and SSc-PAH follows separate, mechanism-directed pathways rather than a single unified approach. For progressive SSc-ILD, mycophenolate mofetil is widely used as first-line immunosuppressive therapy on the basis of randomized trial evidence of efficacy comparable to cyclophosphamide with a more favourable toxicity profile; the antifibrotic agent nintedanib is approved for slowing forced vital capacity decline in SSc-ILD, and the interleukin-6 receptor antagonist tocilizumab has shown benefit in preserving lung function, particularly in patients with elevated inflammatory markers. Cyclophosphamide remains an option for rapidly progressive or severe disease. Combination of an immunosuppressive or antifibrotic agent with structured pulmonary rehabilitation and management of gastro-oesophageal reflux, a recognized contributor to lung injury in SSc, is standard supportive practice.

For confirmed SSc-PAH, treatment now typically begins with upfront combination therapy — most often an endothelin receptor antagonist plus a phosphodiesterase-5 inhibitor — rather than sequential monotherapy, reflecting evidence that combination therapy improves functional class and delays clinical

worsening compared with either drug alone. Prostacyclin pathway agents are added for patients with more severe haemodynamic impairment or inadequate response to dual therapy. Because comorbid ILD or left heart disease can complicate the risk-benefit balance of vasodilator therapy through ventilation-perfusion mismatch, treatment intensity in patients with combined ILD and PAH is individualized, and some clinicians favour a more cautious escalation strategy in this subgroup.

In healthcare systems with constrained access to antifibrotic agents, biologic therapy, or the full range of PAH-targeted drugs — a relevant consideration for rheumatology and pulmonology practice in Uzbekistan — the practical priority is to ensure that structured screening itself is not omitted: serial pulmonary function testing with DLco and echocardiography are comparatively low-cost, widely available investigations that allow early detection and appropriately timed referral even where the newest antifibrotic or prostacyclin pathway agents remain difficult to access.

**Conclusion**

Interstitial lung disease and pulmonary arterial hypertension are now the leading causes of mortality in systemic sclerosis, and although both arise from the same underlying autoimmune and microvascular disease process, they follow distinct pathobiological pathways — predominantly fibrotic in ILD, predominantly vasculopathic in PAH — that demand separate screening tools, diagnostic confirmation, and treatment strategies.

For clinical practice, this translates into two actionable priorities: embedding structured, lifelong pulmonary screening with serial pulmonary function testing and echocardiography into routine SSc follow-up regardless of symptoms, and selecting therapy according to the confirmed mechanism — antifibrotic or immunosuppressive therapy for ILD, combination vasodilator therapy for PAH — rather than a uniform approach. Continued application of these principles, adapted to local resource constraints, holds substantial potential to reduce pulmonary mortality and improve quality of life for patients with systemic sclerosis, including within the healthcare system of Uzbekistan.

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