# Review

# Systemic sclerosis: one year in review 2026

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**ABSTRACT**

*Systemic sclerosis (SSc) is a rare, chronic connective tissue disease characterised by a complex and not yet fully understood pathophysiology, leading to a wide spectrum of clinical manifestations. Despite important advances over recent years in elucidating disease mechanisms, improving early recognition, and expanding therapeutic options, SSc continues to represent a major clinical challenge due to its heterogeneity and unpredictable course. Ongoing research efforts are essential to better define disease subsets, identify prognostic markers, and refine treatment strategies. In this context, this annual review provides a critical overview of the most relevant studies published in 2025, with a focus on advances in pathogenesis, organ involvement, therapeutic approaches, and patient outcomes in systemic sclerosis.*

## Introduction

Systemic sclerosis (SSc) is a rare connective tissue disorder, and its complexity and heterogeneity make it one of the most challenging clinical conditions. Microvascular injury, immune system dysregulation with persistent inflammation and progressive tissue fibrosis appear to drive disease progression and beyond the wide clinical variability of the disease there is a long-term condition associated with a significant deterioration in patients' quality of life. As part of the ongoing "One Year in Review" series by *Clinical and Experimental Rheumatology*, this article provides a narrative and critical appraisal of the most relevant literature on SSc published during 2025. We carried out a Medline search using the term "systemic sclerosis" (MeSH terms and semantic search), with particular attention to studies addressing disease mechanisms, clinical features, treatment strategies, and patient-reported outcomes. We considered English-language original studies involving adult SSc patients published between 1 January 2025 and 31 December 2025. We excluded case reports, and the final studies selection was based on the authors' judgement of clinical relevance, methodological quality, and novelty of the findings.

## Pathogenesis

The past year has witnessed significant strides in deciphering the complex pathogenesis of systemic sclerosis (SSc). By integrating advanced single-cell technologies, spatial omics, and large-scale genomic analyses, researchers have provided new insights into the interplay between innate and adaptive immunity, vascular dysfunction, and fibroblast heterogeneity.

### *Innate immunity and the interferon signature*

A significant advancement involves the role of mitochondrial DNA (mtDNA) as a driver of type I interferon (IFN) signature. Giaglis *et al*. demonstrated that plasma of SSc patients contains highly abundant oxidised mtDNA, whose levels are nearly 152 times higher than in healthy controls (HC). Specifically, oxidised mtDNA from platelets binds CXCL4, and together they stimulate further mtDNA release from neutrophils via neutrophil extracellular traps (NETosis). The authors also showed that SSc plasma-derived mtDNA induces IFN signalling through endosomal TLR9, cGAS/STING, and JAK/STAT pathways, while inhibition of the IFN receptor (IFNAR) or Janus kinases (JAK) can antagonise these pro-NETotic effects. No significant differences were observed across SSc subsets, but plasma mtDNA levels were significantly elevated in SSc pa-

tients with radiographically confirmed interstitial lung disease (ILD) compared to those without (1).

The clinical utility of measuring this IFN activity has been further investigated in dcSSc patients of the US Prospective Registry of Early Systemic Sclerosis (PRESS, incident cohort) and the UK observational cohort (Stratification for Risk of Progression in Scleroderma, STRIKE, prevalent cohort) registries. The authors obtained serum type I interferon score, a six-analyte serum test (measuring CCL2, CCL8, CCL19, CXCL9, CXCL10, and CXCL11) and classified dcSSc patients as IFN-high or IFN-low. Their findings indicate higher IFN score are more common in the early phases of SSc and that IFN-high patients exhibit significantly worse baseline lung function, as measured by FVC and DLCO, and higher overall disability according to the HAQ-DI. Longitudinally, patients with persistently high scores despite immunosuppression showed worse 12-month outcomes and a cumulative 5-year mortality of nearly 25% compared to roughly 9% in those with low scores, suggesting that serum IFN score could be a reliable biomarker for identifying high-risk dcSSc patients (2).

A parallel work by Di Donato *et al*. extended this investigation into a retrospective, longitudinal lcSSc cohort. lcSSc patients also showed higher IFN score values compared to HC. Using a time to clinical worsening (TTCW) endpoint adopted from the MINIMISE trial, they found that a high baseline IFN score conferred an increased risk of meeting major clinical milestones, such as new-onset pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) progression, or SSc-related death. Combining the IFN score with baseline clinical markers like digital ulcers (DUs) and modified Rodnan skin score (mRSS) significantly improved risk stratification, identifying a "high-risk" group with a shorter mean time to clinical worsening (3).

All together these findings support the central role of type I IFN activation as a bridge between innate immune dysregulation and clinical disease progression in SSc. Rather than representing an isolated immune abnormality, the IFN signature appears to integrate upstream triggers, such as mitochondrial damage and genetic susceptibility, with downstream effects on vascular injury and organ involvement. However, most available data derive from observational cohorts and require validation in larger prospective studies.

*Genome*

Ketkar *et al*. utilised an innovative Evolutionary Action-Machine Learning (EAML) framework to move beyond non-coding GWAS hits and identify novel protein-coding variants. This integrative approach identified a novel SSc susceptibility locus at the MICB gene (rs2516497), which was replicated in independent large-scale European cohorts. *MICB* encodes a stress-inducible cell surface molecule that labels cells for targeting by natural killer cells, and its expression in SSc skin was localised primarily to fibroblasts and endothelial cells. Furthermore, the EAML framework prioritised 284 genes enriched in the type I IFN pathway, such as *IFI44L* and *IFIT5*, emphasising the functional impact of rare missense mutations on SSc development (4).

The role of the complement system has also been refined through the work of Martínez-López *et al*. who examined the copy number (CN) variation of *C4A* and *C4B* within the MHC region. Their analysis of over 10,000 SSc patients revealed that a lower total *C4* CN is a significant risk factor across all SSc subgroups. Interestingly, the study identified distinct isotype effects: lower *C4A* CN were more common in diffuse cutaneous SSc (dcSSc) and antitopoisomerase-I (ATA) positive patients, whereas lower *C4B* CN was more strongly associated with the anticentromere (ACA) positivity and limited cutaneous SSc (lcSSc) subtypes. These isotope-specific effects were notably sex-biased, with lower *C4A* showing a stronger impact in males with dcSSc. The findings suggest that *C4A* deficiency may impair the clearance of immune complexes, thereby exacerbating vascular damage in more severe SSc phenotypes (5).

Rosa-Baez *et al*. conducted the largest study to date assessing the *MUC5B* promoter variant (rs35705950), a well-established risk factor for idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis (RA)-ILD. Despite analysing a cohort of over 2,300 SSc-ILD patients, they found no evidence of an association between this variant and SSc-ILD pointing to different origins and mechanisms underlying these ILD (6).

*Vascular dysfunction*

Endothelial damage is recognised as an early event in SSc, and several studies this year have focused on the endothelial-to-mesenchymal transition (EndoMT). Wang *et al*. investigated the role of chitinase 3-like 1 (CHI3L1) in promoting EndoMT in SSc, showing that CHI3L1 levels are significantly elevated in both the serum and skin of SSc patients, where the protein co-localises specifically with the endothelial cell marker CD31. This co-localisation was notably higher in patients with severe vasculopathy, such as DUs. Furthermore, the authors showed a strong correlation between circulating CHI3L1 concentrations and the vascular injury marker endothelin-1 (ET-1), suggesting that CHI3L1 is a key player in early microvascular damage. Mechanistically, a proteomic analysis demonstrated that CHI3L1 acts by binding to the CD44 receptor on endothelial cells, an interaction that triggers the Akt/mTORC1/S6K signalling axis, regulating the expression of transcription factors like Snail and Slug, which are primary drivers of the EndoMT process. In human endothelial cell cultures, CHI3L1 stimulation led to a distinct phenotypic shift: cells lost their specific endothelial markers (CD31 and VE-cadherin) and acquired myofibroblast-like characteristics. Importantly, the study found that this profibrotic transition could be effectively inhibited in vitro by using CHI3L1-neutralising antibodies, blocking the CD44 receptor, or inhibiting mTORC1 with rapamycin (7).

*Fibrosis*

Advancements in spatial multiomics have provided a much clearer picture of the fibrotic microenvironment. Li

*et al*. used spatial transcriptomics in skin biopsy samples of dcSSc patients to identify 12 different clusters of cell type niches. Among these, "niche 0" was identified as a disease-specific fibrotic hub uniquely enriched with fibroblasts, macrophages, conventional dendritic cells, and mast cells. Notably, the proportion of this niche showed a strong positive correlation with clinical indicators of severity, such as mRSS, C-reactive protein (CRP) levels, and platelet counts. Moreover, the authors showed a significant reduction in myofibroblast progenitors and a corresponding expansion of terminally differentiated myofibroblasts. This transition was linked to a failure of a specific regulatory mechanism involving ACKR3, a CXCL12 decoy receptor normally expressed on progenitors to limit leukocyte recruitment. As progenitors differentiate, ACKR3 expression is lost, leading to uncontrolled CXCR4-mediated infiltration of pro-inflammatory macrophages. Spatial analysis confirmed that these pro-inflammatory macrophages accumulate in the immediate proximity of fibroblasts, sustaining a "vicious cycle" of inflammation-driven fibrosis. Finally, they demonstrated that the proportion of niche 0 was significantly higher in the samples of dcSSc patients with rapid skin fibrosis progression and significant refractoriness to standard treatment with mycophenolate mofetil (MMF) (8).

Clark *et al*. expanded the understanding of fibroblast heterogeneity by demonstrating the presence of a non-migratory resident population of fibroblasts. The authors showed that in dcSSc patients migratory fibroblasts are characterised by high contractility and motility, with high activity in early-stage dcSSc, and are strongly responsive to TGF-β signalling. In contrast, the newly characterised nonmigratory resident fibroblasts persisted in the dermal matrix throughout all disease stages, including late-stage dcSSc, and displayed NF-kB and IL-17 signalling, and overexpressed chemokines such as CCL2, CXCL12, and CCL19. Crucially, resident fibroblasts showed a unique profibrotic response to the chemokine CCL2 (MCP-1), which increases their expression of α-SMA, a response much less pronounced in migratory cells. Spatial analysis localised these resident fibroblasts (CD90+) primarily within the deeper dermis, suggesting a model where migratory fibroblasts drive early tissue deposition, whereas nonmigratory resident fibroblasts regulate persistent inflammatory cell recruitment (9).

Another study by Fang *et al*. focused on the immunomodulatory role of fibroblasts by investigating prostaglandin D2 synthase (PTGDS). High-resolution single-cell analysis and validated immunohistochemistry revealed that PTGDS expression is significantly elevated in SSc skin, specifically localised within dermal fibroblasts. In SSc samples, approximately 40% of total fibroblasts were PTGDS-positive, compared to only 15% in HC. Functional profiling classified these cells as a pro-inflammatory fibroblast subset characterised by a gene signature enriched for leukocyte migration and chemotaxis. Further subset analysis showed a distinct preference for the Th2 lineage, with migrated T cells showing significant upregulation of Th2-defining markers such as GATA3, IL-4, and IL-13. This pathological transition could be effectively reversed *in vitro* using AT56, a selective PTGDS inhibitor. In human cell cultures, AT56 reduced extracellular PTGDS levels and the recruitment of Th2 cells (10).

Differential mechanisms were also explored by Huang *et al*. who compared skin biopsy samples from localised scleroderma (LoS) patients with SSc patients. Using scRNA-seq, they found that LoS samples are characterised by the formation of tertiary lymphoid structures (TLS) in the dermis, with the presence of T follicular helper (Tfh) cells and B cells. In contrast, fibroblasts overexpressing CREB3L1 were more common in SSc samples (11).

Another marker, interleukin-40 (IL-40), was explored by Navrátilová *et al*. IL-40, a B-cell-associated cytokine, was found elevated in the serum and involved skin of SSc patients, where it was expressed primarily by immune cells and fibroblasts. Serum IL-40 levels correlated with disease activity (ESSG index), gastrointestinal involvement (specifically constipation and dysphagia), and levels of TGFβ1 and IL-8. *In vitro* experiments showed that SSc PBMCs release IL-40 in response to TGFβ1 and IL-4, and that extracellular IL-40 in turn stimulates the secretion of IL-6 and MCP-1 (12).

Ferraz-Amaro *et al*. explored the clinical significance of neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, in a cross-sectional study involving 81 patients with SSc and 76 controls. The authors found that, while absolute serum NGAL levels did not differ significantly between the two groups, they were independently and positively associated with mRSS. Furthermore, the study identified NGAL as a significant marker of metabolic syndrome features, being associated with a pro-atherogenic lipid profile, with higher LDL:HDL and apolipoprotein B: A1 ratios and a higher atherogenic index, as well as a reduction in insulin sensitivity (13).

Ueberall *et al*. utilised a type I collagen-based 3D matrix model to investigate how the biomechanical properties of the extracellular matrix (ECM) regulate fibroblast dynamics SSc. By integrating bulk RNA sequencing with single-cell and spatial transcriptomics, the authors demonstrated that increased matrix stiffness promotes the differentiation of PI16+ progenitor-like fibroblasts into a profibrotic population of SFRP2+COMP+PU.1+myofibroblasts. Moreover, pharmacological inhibition of FAK was shown to disrupt this stiffness-induced myofibroblast activation. Spatial mapping further revealed that these subsets colocalise within high-stiffness, ECM-dense regions of the skin (14).

Therefore, SSc fibrosis is not a "simple" fibroblast-driven process, but rather a complex interplay between immune cells, fibroblast subsets, and the extracellular matrix.

### *Immune cell abnormalities and organ involvements*

Research into specific immune cell populations has revealed subsets linked to severe complications, with Shim-

agami *et al*. providing a breakthrough in understanding the myeloid drivers of scleroderma renal crisis (SRC). By conducting single-cell profiling of PBMCs from immunosuppressive therapy-naïve patients, the researchers identified a distinct population of EGR1+ CD14+ monocytes that is specifically enriched in the peripheral blood of patients with SRC. These monocytes exhibit a unique molecular signature characterised by activated NF-κB and type I/II interferon signalling, which are likely induced by SRC-associated systemic factors such as angiotensin II and ischaemia-related damage-associated molecular patterns (DAMPs). Functional trajectory analysis demonstrated that these circulating EGR1 + monocytes differentiate into tissue-damaging macrophages, characterised by high expression of THBS1 (thrombospondin-1), IL1B, and LRG1. Crucially, the study revealed that EGR1 expression in monocytes is highly dynamic, with higher levels at the onset of SRC and a significant decline following treatment and clinical improvement. Furthermore, the proportion of this monocyte subset positively correlates with systolic blood pressure and mRSS. Regarding SSc-ILD, the same study identified a significant expansion of effector memory CD8+ T cells characterised by high expression of type II interferon-stimulated genes (ISG). Trajectory analysis revealed that these cells possess a high migratory capacity, mediated by CXCR3 and CCR5, suggesting they migrate from the blood to the lungs. Spatial analysis confirmed that similar "Type II ISG-high" T cells infiltrate fibrotic lung tissue, suggesting that the detection of this subset of effector memory CD8+ T cells cells could play a significant role in lung disease progression (15).

In the context of SSc-ILD, Smith *et al*. focused on circulating monocytes and monocyte-derived macrophages (MDMs) in patients with progressive ILD. They discovered that patients with progressive SSc-ILD have a significantly higher percentage of hybrid TLR4+ M2 monocytes in their blood compared to those with stable or no ILD. When cultured, these monocytes from progressive SSc-ILD patients differentiated into macrophages with a markedly enhanced profibrotic phenotype, showing significantly increased gene expression and protein synthesis of TGFβ1, MerTK, CD206, and CCL18 (16).

Complementing this, Ehlers *et al*. conducted a systematic analysis of the T-cell compartment, comparing peripheral blood molecular signatures with the local lung microenvironment accessed via bronchoalveolar lavage (BAL) of SSc-ILD patients. In the peripheral blood, the researchers identified a significant accumulation of CD4+ terminally differentiated effector memory (TEMRA) cells, a subset associated with immunosenescence, an "exhausted" phenotype, characterised by the high expression of PD1 and the loss of CD28 costimulation. By utilising mitochondrial-specific dyes (MitoSpy), the authors demonstrated that circulating T cells from SSc-ILD patients (both CD4+ and CD8+ subsets) showed a reduction in functional mitochondria compared to healthy individuals. The study also found localised abnormalities in BAL-derived lymphocytes that were not present in the blood, such as CD8+ T cells with an exhausted phenotype characterised by the co-expression of PD1 and CD69. These exhausted cells were found in association with highly activated type 2 conventional dendritic cells (cDC2s), known stimulators of Th2-type immune response (17).

Further insights into SSc-ILD were provided by Assassi et al. through a comprehensive analysis of the placebo arm of the SENSCIS trial. Utilising global RNA sequencing of PBCs, the authors examined 62 curated transcript modules to determine their significance for FVC decline over 52 weeks, showing that higher baseline modular scores for myeloid lineage are associated with a faster decline in predicted FVC%, regardless of MMF treatment. Notably, these transcript modules showed only a weak correlation with serum CRP. Conversely, the authors identified a different set of predictive biomarkers specific to MMF response, such as higher baseline scores in lymphoid lineage and mitochondrial modules (18).

**Take home messages**

- Oxidised mitochondrial DNA may contribute to the type I IFN signature in SSc, triggering inflammation and fibrosis. Preliminary data suggest that serum IFN score may provide a promising risk stratification biomarker. Patients with persistently high IFN scores, particularly those with early-stage diffuse SSc, have significantly worse baseline lung function and are at a much higher risk of disease progression, increased overall disability and long-term mortality (1, 2).
- Recent genomic advancements have identified new susceptibility loci and provided further insights into the role of the complement system in SSc. A new variant in the MICB gene demonstrates the effect that rare mutations can have on disease development (4). Furthermore, a reduced number of complements C4 molecules exacerbates vascular damage, potentially by impairing the efficient clearance of immune complexes (5).
- Endothelial-to-mesenchymal transition seems to play a key role in the initial phases of microvascular damage, with CHI3L1 emerging as a potential mediator of this process (7).
- Specific immune cell profiles have been associated with severe SSc complications. According to preliminary data EGR1+ circulating monocytes may contribute to scleroderma renal crisis (15). Moreover, myeloid gene signatures, hybrid TLR4+ monocytes and exhausted mitochondria-deficient T cells infiltrating the lungs seem to powerful predictors of rapid fibrotic progression and declining FVC (16).

## Clinical manifestations

*Peripheral vasculopathy*

Microangiopathy is a defining feature of SSc. Raynaud's phenomenon (RP) is one of the earliest clinical expressions of the disease and serves as a key sentinel sign for the identification of very early SSc (VEDOSS). Despite its straightforward clinical recognition within rheumatology, its objective quantification remains limited. A UK study enrolled 45

patients with RP and developed an artificial intelligence-based Raynaud's quantification index (ARTIX), a digital tool enabling objective self-quantification of RP severity through mobile phone photography. The index was validated against thermography during cold challenge testing in primary and secondary RP patients and HC. RP patients showed significantly lower ARTIX values compared with HC both at baseline and across all time points during cold exposure, in agreement with thermographic assessments. Higher ARTIX scores were observed in males and in patients receiving vasoactive therapy, whereas lower values were associated with a late capillaroscopic pattern, diffuse cutaneous SSc, and ACA negativity (19).

The most severe complication of microvascular involvement is DUs development. Data from the SCLEROCAP study demonstrated that digital artery disease contributes independently of microangiopathy to DU development, supporting the complementary role of laser Doppler assessment alongside capillaroscopy for improved risk stratification (20). Furthermore, isolated cryofibrinogenemia has been identified in a subset of SSc patients and has been shown to be associated with a more severe microvascular phenotype, increased risk of mortality, and higher incidence of digital amputation, suggesting a marker of greater systemic vascular involvement (21).

*Heart involvement*

Primary cardiac involvement in SSc (SSc-pHI) represents a major determinant of mortality, encompassing a spectrum from subclinical diastolic dysfunction to life-threatening conditions such as myocardial ischemia and cardiogenic shock. A large study established that risk factors for SSc-PHI include age, male sex, swollen joints, skeletal muscle weakness, tendon friction rubs, telangiectasia, intestinal symptoms and anti-topoisomerase I antibodies. Survival is significantly reduced in patients with SSc-pHI compared to those without and is also lower than in patients with ILD (22).

Cardiogenic shock is among the most severe complications. In an observational cohort of 10 SSc patients admitted with acute ventricular dysfunction and without prior heart disease, all presented with elevated troponin levels (2077±3379 ng/L), and pericardial effusion, with 30% of them requiring pericardiocentesis. Cardiac magnetic resonance (MR) and biopsy findings were consistent with myocarditis characterised by T lymphocyte and macrophage infiltration. In-hospital mortality reached 60% (23).

In clinical practice, it is useful to have predictive biomarkers of cardiac involvement (such as NT-proBNP and troponin I). In a German study, serum sIL-2R levels, analysed in 315 SSc patients, were associated with T-cell activation, cardiac involvement, and disease progression. Patients with cardiac involvement showed higher sIL-2R concentrations, which decreased with clinical improvement. Levels ≥900 U/ml identified more active disease and predicted early progression (24).

Cardiovascular risk in SSc is also driven by chronic inflammation and accelerated atherosclerosis, which leads to an increased frequency of cardiac events. In a cohort of 360 patients, 17.8% experienced major cardiac events (MCEs) (including myocardial infarction, peripheral vascular disease and stroke). Avascular areas at nailfold capillaroscopy were independent predictors of MCEs, whereas microhaemorrhages showed a protective trend, supporting the prognostic role of NFC in risk stratification (25).

*Pulmonary arterial hypertension*

PAH develops in 6-12% of patients with SSc. Despite often presenting with milder haemodynamic impairment, patients with SSc-PAH have a worse prognosis and respond less favourably to treatment compared with those with idiopathic PAH (IPAH). It is well known that early diagnosis with screening strategies of PAH may allow prompt treatment at an earlier stage of the disease, when therapies are most effective. Among the proposed screening tools, the DETECT algorithm is a forward stepwise procedure designed for patients with SSc to be referred to right heart catheterisation (RHC), because it can be of aid in identifying early SSc-PAH patients but also discriminating patients with a low-risk profile from those at higher risk of developing PAH. A recent study evaluated the risk of PAH development in 131 SSc-patients estimated according to the DETECT algorithm, which assesses the likelihood of PAH using a multifactorial approach, by combining different parameters (FVC/DLCO ratio; serum urate; NT-proBNP; telangiectasias; ACA, SSc-specific parameters associated with higher PAH risk; right axis deviation on electrocardiography), then some echocardiographic values, such as right atrium area (RA) and tricuspid regurgitation velocity (TRV), and finally performing RHC at SSc patients with high-risk for PAH diagnosis. At the same time, the risk of PAH development was estimated according to the 2015 European Society of Cardiology and European Respiratory Society (ESC/ESR) guidelines which stratify patients through echocardiographic parameters, such as VTR (the 2022 updated ESC/ERS guidelines were still not applicable, as the screening phase was conducted before their release). The DETECT algorithm showed higher sensitivity (96% *vs*. 75%) and negative predictive value (99% vs. 93%) but lower specificity (77% *vs*. 88%) and positive predictive value (53% *vs*. 64%) for PAH diagnosis compared to the 2015 ESC/ERS guidelines. During the follow-up, a total of 24 patients with SSc died, and 6 of them died from complications of PAH, with a 5-year survival rate of 81.7%. Of those 79 patients with SSc negative at baseline for PAH screening with both strategies, 70 (88.6%) were still alive, and none of them developed PAH. Through this study, Stano et al. found that the DETECT algorithm had a high sensitivity and negative predictive value in screening patients with SSc, strongly supporting its use in clinical practice (26).

Taking a closer look at screening tools, doppler echocardiography, whilst being a useful and standardised tool for screening for PAH, its accuracy is still suboptimal. In this context, there is a growing awareness of the importance of right atrial function in PAH. Notably, it has been suggested that right atrial reservoir

strain (RARs) may be compromised already in the early stages of PAH because of an increased right ventricular (RV) diastolic pressure. Codullo *et al*. tested the hypothesis that RARs might be a sensitive parameter to reflect an initial overload of the right heart and predict the development of PAH, by enrolling SSc patients who underwent a complete echocardiographic examination which included the estimate of systolic pulmonary artery systolic pressure (PAPs), the tricuspid annular plane systolic excursion (TAPSE), its ratio (TAPSE/PAPs) and RARs. During a subsequent median follow-up period some selected patients underwent to RHC according to a multidisciplinary approach of risk assessment of PAH, which was confirmed in 10/11 patients. At multivariable analysis, RARs was the only echocardiographic parameter with a statistically significant and an independent predictive accuracy for PAH, supporting its use as a good relevant imaging parameter during echocardiographic screening examinations of PAH in patients with SSc (27).

In a similar setting, Egberts *et al*. evaluated the potential role of right ventricular free wall systolic strain (RVFWSS) in the early detection of PAH. Through a retrospective analysis of echocardiographic data from SSc patients who underwent routine PAH screening, RVFWSS demonstrated a good correlation to RHC data (higher prevalence of abnormal RVFWSS in a group of patients who screened positive at ASIG screening algorithm and had PAH consequently confirmed by RHC). Furthermore, RVFWSS abnormalities preceded a formal PAH diagnosis by an average of 29 months, suggesting RV dysfunction emerges well before overt haemodynamic changes, highlighting the significant role of RVFWSS as an early biomarker for PAH in patients with SSc. This study showed how incorporating RVFWSS into the Australian Scleroderma Interest Group (ASIG) screening algorithm increase the positive predictive value for PAH diagnosis, while maintaining a high negative predictive value, potentially reducing unnecessary RHC (28).

The 2022 ESC/ERS guidelines for PAH, along with the updates from the Seventh World Symposium on Pulmonary Hypertension (WSPH), underscore the importance of risk stratification to predict mortality risk and guide treatment decisions. In a recent study of Bjørkekjær *et al*. SSc-PAH patients were included, and the risk was assessed using several established PAH risk models, like the ESC/ERS three-strata model, which combines up to 18 risk parameters to define low-, intermediate- or high-risk status with estimated 1-year mortality rates. At follow-up, a simplified four-strata model based on WHO functional class, 6-minute walk distance and brain natriuretic peptide (BNP) or N-terminal-proBNP was performed by categorising risk as low, intermediate-low, intermediate-high or high. The study evaluated both baseline risk assessment and follow-up risk stratification, examining their association with overall survival. The guideline-recommended ESC/ERS three strata model showed lower predictive ability for mortality than more refined multiparametric approaches, like the ESC/ERS four strata model, which demonstrated superior mortality prediction. Overall, the study demonstrated that multiparametric risk stratification models derived from PAH guidelines can be applied to SSc-PAH populations (29).

*Lung involvement*

Lung involvement is the main cause of morbidity and mortality in SSc, including lung fibrosis or ILD. Screening and monitoring SSc-ILD is essential in the care of SSc patients, as the course of SSc-ILD course is variable and highly heterogeneous with many patient reported outcomes, such as recent worsening of dyspnoea, is as important as more complex, clinical and instrumental assessment with many patients experiencing stable lung function or a slow progression over time defined using spirometry parameters and/or extent of ILD on high-resolution computer tomography (HRCT). Morrisroe *et al*. sought to determine the prognostic significance of patient reported worsening dyspnoea in isolation and alongside the current definitions of progressive SSc-ILD according to American Thoracic Society (ATS) guidelines 2022 (worsening respiratory symptoms together with physiological evidence of disease progression defined as an absolute decline of ≥5% in FVC predicted or an absolute decline in diffusing capacity for carbon monoxide (DLCO) corrected for haemoglobin ≥10% predicted within a 12-month period over follow up and /or radiological progression of fibrosis on HRCT scan) and INBUILD trial definition (decline in FVC ≥10%, OR FVC >5% but <10% with worsening respiratory symptoms or extent of ILD on HRCT, or worsening respiratory symptoms with worsening extent of ILD on HRCT over a 24-month period). INBUILD criteria have not the same significance of ATS criteria, since ATS sort out a population showing higher mortality as compared to the rest of ILD, unlike INBUILD criteria where mortality is unchanged. Patient reported outcomes, such as recent worsening of dyspnoea, is as important as more complex, clinical and instrumental assessments, since is associated with higher mortality (30). The choice of progression criteria sharply influences the population selected, with a direct impact on the comparability of data, since different criteria show limited correlation with each other. This variability underscores the need for standardisation of progression definitions. In clinical practice, broader criteria allow wider access to treatment in patients with longstanding disease, whereas in early disease, shorter interval progression criteria enable the timely identification of individuals at higher risk who may benefit most from aggressive, combined therapeutic strategies. Hoffmann-Vold *et al*. demonstrated that SSc-ILD progression does not predict further ILD progression at a next annual follow-up visit, but progression is associated with mortality. These results have implications for clinical practice because they support a paradigm shift in treatment strategy, advocating for initiating therapy in patients at risk of progression (31). There is still no consensus on disease severity, progression, and outcome definitions for SSc-ILD and several studies based on FVC measured by spirometry, and DLCO as outcome measure have been conducted in recent years. However, in the early phase of SSc-ILD, FVC

and DLCO can be normal. Chaigne *et al*. demonstrated that patients with either reduced TLC values at baseline (*e.g*. below 80%) or a decline in the same value longitudinally over time, or both, correlate with lower survival rates and a higher risk of new onset of ILD or lung fibrosis. Furthermore, a decrease in TLC is predictive of FVC and DLCO decline in SSc (a 10% TLC decrease was associated with a 5% FVC or a 10% DLCO) (32).

The role of HRCT in the screening and diagnosis of SSc-ILD is well established, and its repeated use represents an effective strategy for disease monitoring. In a recent study of Tschalèr *et al*. the semi-quantitative HRCT scoring method has been validated for the assessment of ILD severity and progression in systemic sclerosis, demonstrating good feasibility and excellent inter- and intra-observer reproducibility. Importantly, the extent of fibrosis assessed on HRCT correlated with pulmonary function parameters such as FVC, DLCO, and exercise-induced oxygen desaturation, supporting its clinical relevance and showing additive value of structural to functional ILD assessment (33).

LUS has emerged in recent years as an easily accessible and valuable method for the investigation of SSc-ILD. It showed high accuracy in identifying SSc-ILD compared with the gold standard of HRCT. Key LUS findings are represented by the sonographic artefacts of B-lines (BLs) and pleural line irregularity (PLI), the definition of which has recently undergone standardisation by the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group. Beigi *et al*. demonstrated correlations between LUS and automated quantitative computed tomography (qCT) measurement of ILD extent, including both superficial and deeper lung involvement. In this study total BLs number was collected (from 0 to 140), PLI score was applied (from 0 to 28) and CT scans were performed in order to document presence of ≥10% ILD, as well as an ILD-pattern, such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) or organising pneumonia (OP). Quantitative LUS BLs and PLI score correlated with qCT-defined ILD extent (ground-glass opacities, reticulations and fibrosis volumes), especially at lung bases, as assessed by three-levels qCT analysis, where basal BLs correlated with basal lung surface and core ILD, whereas PLI score correlated with the whole-lung surface ILD volume and with core ILD of lung bases and midfields. LUS scores (particularly the novel PLI score) were found to correlate with deeper ILD volume, suggesting potential to overcome traditional LUS limitations related to superficial lung assessment (34).

*Skin involvement*

Skin fibrosis is a defining feature of SSc, and its extent reflects both disease severity and internal organ involvement. Because cutaneous changes are central to the clinical phenotype, improving how skin involvement is measured has become a key focus, prompting the development of more refined diagnostic approaches. In this context, high frequency ultrasonography (HFUS - 18 MHz) has emerged as a potential alternative to RSS for quantifying dermal involvement. In a pilot cross-sectional study, dermal thickness at the left index finger was compared between 63 patients and 48 healthy controls, showing a clear separation between groups. The authors propose a 1.5mm cut-off as a pragmatic discriminator for routine use, noting that HFUS is reproducible, requires minimal training, and may overcome the limitations of palpation-based scoring (35). The study remains preliminary, and broader validation in prospective multicentre cohorts is needed to confirm its utility and generalisability. Another study by Desai *et al*. evaluated the validity of US against clinical, histologic, and molecular benchmarks. Despite its comprehensive design, results were largely negative. Except for the hand region, US measures did not reliably distinguish affected SSc skin from healthy controls, and correlations with mRSS were only weak to moderate. Criterion validity was also limited: USbased dermal thickness correlated only modestly with histologic thickness and showed no association with collagen density or fibrosis-related gene expression (36). Overall, these findings temper the optimism of earlier pilot works and highlight the need for more advanced, biologically informed imaging tools capable of capturing both clinical severity and underlying tissue pathology in SSc.

*Gastrointestinal involvement*

The involvement of the gastrointestinal (GI) tract is extremely common in SSc, potentially affecting any segment and often impairing quality of life. Because GI manifestations may arise early, vary widely by location, and can even remain clinically silent, a systematic evaluation is essential in all patients. In a very large EUSTAR cohort of more than 5400 patients with SScILD, gastroesophageal reflux (GERD) was reported in over 80% of cases, confirming its exceptional frequency in this population. Patients with GERD displayed a consistently more severe disease phenotype, with a higher prevalence of diffuse cutaneous involvement and more advanced lung impairment. Although GERD itself did not influence progression free survival compared with non-GERD patients, its presence appeared to mark a subgroup with more severe systemic and pulmonary involvement (37). The strength of this study lies in its unprecedented sample size, allowing a robust characterisation of the SScILD phenotype associated with GERD and supporting its potential role in risk stratification.

In a 20-year single-centre case-control study, 42 SSc patients hospitalised for lower GI involvement were compared with matched SSc controls to identify factors associated with severe lower tract disease. Affected patients showed marked systemic severity, and multivariable modelling identified five independent predictors (BMI, cardiomyopathy, albumin, hsCRP and haemoglobin) which were incorporated into a clinical risk model that demonstrated excellent discrimination (AUC 0.93) and good internal calibration (38). Despite its small, single-centre design, the study provides an initial framework for identifying patients at higher risk of severe lower GI involvement and supports the development of prospective cohorts to

refine prediction and better understand pathogenesis.

Malnutrition represents a critical downstream consequence of GI involvement in SSc and is increasingly recognised as a major determinant of prognosis. In a large cohort of over 1900 patients, 43% met the GLIM (Global Leadership Initiative on Malnutrition) criteria for malnutrition, and one-third of these had severe forms. Malnourished individuals displayed a more aggressive systemic phenotype, with higher rates of GI manifestations, cardiopulmonary disease, systemic inflammation, hypoalbuminemia and anaemia. Upper GI symptoms were independently associated with malnutrition, underscoring the clinical relevance of oesophageal dysfunction and impaired intake. Importantly, malnutrition correlated with poorer quality of life, reduced physical function and significantly worse survival, even after adjustment for age, sex and disease subset (39). These findings highlight malnutrition as a frequent, clinically meaningful complication of SSc-related GI disease and support early nutritional assessment and referral as integral components of comprehensive care.

*Other involvements*

Beyond the major organ systems traditionally emphasised in SSc, several additional manifestations remain underrecognised and poorly investigated, despite their potential clinical relevance. Three recent studies illustrate how seemingly disparate areas of involvement can reveal important aspects of disease burden and reinforce the need to maintain close attention on less prominent yet equally relevant manifestations of SSc.

Data from two large early-SSc cohorts showed that more than one-third of patients did not present with RP as their initial manifestation. Puffy fingers/hands were the most common non-RP onset feature, particularly among Black patients. These individuals displayed a more severe phenotype at the enrolment, with more diffuse cutaneous involvement, joint contractures and a higher prevalence of RNA polymerase III positivity (ARA) (40). These findings underscore that early SSc may emerge through pathways other than RP, and that such presentations often signal a more aggressive disease course. Puffy fingers or hand swelling, even without RP, should therefore prompt consideration of early SSc and appropriate autoantibody testing.

In a large case-control study using quantitative sensory testing, peripheral sensory neuropathy (PSN) of the feet emerged as a highly prevalent and substantially under-recognised manifestation of SSc. More than 85% of patients showed objective sensory impairment, involving both small and large fibres, with over half exhibiting combined involvement. PSN correlated with age, smoking, disease duration, corticosteroid use and foot ulceration. Importantly, most patients with PSN reported neuropathic symptoms, and those with symptomatic neuropathy experienced worse physical function, greater foot disability and poorer quality of life. Notably, nearly one in five patients with objectively proven PSN were asymptomatic, underscoring how easily this manifestation can be missed in routine care (41). These findings position foot PSN as a common, disabling and often overlooked component of SSc, supporting the need for systematic sensory assessment within the standard clinical workup.

In a multicentre retrospective series of 223 patients with SRC, late onset SRC, occurring more than five years after SSc diagnosis, accounted for nearly one quarter of all cases, with a mean onset 12 years into the disease course. Compared with early onset SRC, late cases showed a marked male predominance and were more frequently associated with prior corticosteroid exposure, while autoantibody profiles and clinical outcomes were similar across groups (42). These findings challenge the traditional view of SRC as an early complication and demonstrate that clinically significant renal crises continue to occur well beyond the early disease window. The data reinforce the need for ongoing vigilance for SRC irrespective of disease duration, particularly in patients receiving steroids, to ensure timely recognition and management.

**Take home messages**

- Peripheral vasculopathy in SSc encompasses heterogeneous yet prognostically meaningful manifestations: AI-based tools such as ARTIX enable objective quantification of RP, combined laser Doppler and capillaroscopy improve risk stratification for digital ulcers, and severe phenotypes like cryofibrinogenemia identify patients with markedly increased mortality and amputation risk (19).
- Cardiac involvement in SSc is a major determinant of prognosis: primary cardiac disease carries survival rates lower than ILD and is associated with anti-topoisomerase I antibodies and male sex (22); cardiogenic shock shows extreme mortality and a myocarditis like inflammatory infiltrate (23); serum sIL2R ≥900 U/ml identifies patients at risk of early cardiac progression (24); and avascular areas on nailfold capillaroscopy independently predict major cardiac events (25).
- Early identification and accurate risk stratification of SScPAH are improving: the DETECT algorithm offers superior sensitivity and negative predictive value compared with ESC/ERS guidelines (26); right atrial reservoir strain and RV free wall strain abnormalities serve as early echocardiographic markers that precede clinical PAH by years; and, once PAH is established, the ESC/ERS four strata model provides more refined mortality prediction than the traditional three strata approach (27, 29).
- Lung involvement in SSc requires early recognition and multidimensional assessment: patient reported worsening of dyspnoea is a strong mortality predictor even in the absence of physiological decline; prior ILD progression forecasts mortality rather than future functional deterioration, supporting early treatment in at risk patients (30, 31); baseline or declining TLC correlates with survival and anticipates FVC/DLCO worsening (32); and both semiquantitative HRCT scoring and lung ultrasound (PLI score) provide validated tools for evaluating disease severity (34).

- Gastrointestinal involvement in SSc is frequent and prognostically relevant: GERD affects the vast majority of patients with SSc-ILD and marks a more severe systemic and pulmonary phenotype (37); a composite profile including BMI, cardiomyopathy, albumin, hsCRP and haemoglobin accurately identifies those at risk of severe lower GI complications (38); and malnutrition, present in nearly half of patients by GLIM criteria, is strongly associated with reduced survival and impaired quality of life (39).
- Non-Raynaud onset is common in early SSc and puffy hands, particularly in Black patients, may signal a more aggressive phenotype (40); peripheral neuropathy affects the vast majority of patients, often silently, warranting routine screening due to its impact on quality of life (41); and renal crisis can occur late, with a quarter of cases arising more than five years after diagnosis, underscoring the need for lifelong vigilance (42).

**Treatment**

In 2025 the ERS (European Respiratory Society)/EULAR guidelines for connective tissue disease (CTD)-associated ILD were published, providing updated therapeutic recommendations for SSc-ILD. According to the guidelines MMF, rituximab (RTX) and cyclophosphamide (CYC) are conditionally recommended for patients with SSc, as they demonstrated modest benefits in preserving lung function and improving skin involvement, and tocilizumab (TCZ) is strongly recommended for patients with early, inflammatory dcSSc-ILD, based on its ability to stabilise pulmonary function and improve systemic disease features. Nintedanib (NTD) is conditionally recommended for SSc-ILD, particularly in patients with more than 10% extent of fibrotic involvement, although its use is frequently associated with GI adverse events (AEs) (43).

*Immunosuppressants*

Freund *et al*. recently confirmed the stabilisation of pulmonary function tests (PFTs) in SSc patients treated with immunosuppressive drugs, mainly MMF. In these patients, the authors showed an improvement in HRCT finding confirming immunosuppressants a cornerstone in the management of SSc (44). Still regarding the use of immunosuppressive therapies, in the study by Hiura *et al*. RTX and CYC showed comparable improvements in FVC and similar reductions in serum Krebs von den Lungen-6 (KL-6) levels at both 6 and 12 months in patients with SSc-ILD. Overall, the safety profiles of the two treatments were also comparable (45).

Also, a multicentre real-world study including 152 patients with SSc (77.7% with dcSSc subset) supported the effectiveness of RTX in clinical practice. In this cohort, progression of ILD was the most frequent indication for initiating therapy, followed by worsening skin fibrosis and inflammatory arthritis. During the follow-up, many patients required lower RTX dosing (to a single 1000 mg infusion in 22.4% patients and to a single 500 mg infusion in 3.5%) due to favourable clinical response, which also represented the most common reason for treatment discontinuation. The second most frequent cause of stopping therapy was inadequate response, observed particularly in ACA positive and ATA negative patients (46). To note that in this last study about 70% of patients were still on background disease-modifying antirheumatic drug (DMARD) treatment, mainly MMF or MTX at baseline. In this context, another multicentre study conducted in France compared SSc patients treated with MMF (50 subjects), RTX (30) or MMF in combination with RTX (47). The multivariate inter-group analysis showed an association of the combination therapy with a higher skin and/or lung improvement compared with monotherapy groups. These benefits were particularly evident if the two therapies are initiated concurrently early. Regarding safety, AEs were more frequent in the combination cohort (primarily infections), although differences were not statistically significant (47).

The use of a machine-learning causal tree approach enabled a post-hoc analysis of the DESIRES trial to identify predictors of response to RTX, allowing stratification of SSc into distinct phenotypes with different responses to B-cell depletion therapy. Data from this analysis suggested CRP and KL-6 as the main variables stratifying treatment response. Patients with higher CRP levels showed the most pronounced benefit from RTX, with significant improvement in FVC compared with placebo at 24 weeks. Therefore, this phenotype seemed to be the most responsive to B-cell depletion therapy. In contrast, patients with low CRP but elevated KL-6 showed only modest, non-significant differences between treatment arms, while those with low levels of both biomarkers exhibited stable lung function over time and appeared to have a low risk of disease progression (48).

Regarding the use of Janus Kinase inhibitors in SSc, a 24-week randomised study evaluated therapeutic benefit and safety of baricitinib (2 mg and 4 mg daily) in patients with SSc. The authors enrolled 48 patients reporting that the dose of 4 mg led to a significantly greater reduction in skin fibrosis (mRSS) at 12 weeks compared with control, while the 2 mg dose showed more modest effects. Improvements in global response score and quality of life were observed but without statistical significance. Lung function (particularly FVC) showed a numerical increase in the 4 mg group over 24 weeks. Therefore, this study suggested a manageable safety of baricitinib with promising efficacy on skin fibrosis, particularly at 4 mg, probably due to its influence on immune and inflammatory pathways (49).

In SSc, the use of glucocorticoids (GCs) should generally be avoided due to their association with an increased risk of AEs, particularly the potential to precipitate SRC. Mongin *et al*. evaluated if the addiction of oral GCs to immunosuppressant drug may improve skin involvement in early dcSSc patients from the European Scleroderma Trials and Research Group (EUSTAR). The authors evaluated 208 matched patients at baseline and after a follow-up of about 12 months dividing the popu-

lation in two groups: patients treated with oral GCs (≤20 mg/day prednisone equivalent) and immunosuppressive therapy and those receiving only immunosuppression. At approximately 12 months, both groups showed a similar reduction in skin thickness (mRSS), with no significant differences between treatments. In addition, no differences were observed in the occurrence of renal crisis (50). Similar findings of a lack of meaningful efficacy of corticosteroids in early SSc have been reported in another study, whose primary aim was to evaluate capillaroscopic changes following treatment with intravenous corticosteroids over a 3-month period. The authors also assessed disease progression at 52 weeks evaluating LFTs, HRCT and echocardiography. The study included 30 patients with puffy fingers of recent onset (<3 years), disease-specific autoantibodies, and fulfilment of the VEDOSS criteria; of these, 9 patients received intravenous methylprednisolone (1000 mg), while 9 were treated with placebo (51).

*Antifibrotics*

Nintedanib (NTD) has emerged as an antifibrotic agent for SSc-associated ILD with growing evidence supporting its clinical utility in recent studies.

A multicentre study evaluated the efficacy and safety of NTD in patients with CTD and progressive pulmonary fibrosis (PPF). the authors enrolled a total of 66 patients, of whom 35 had SSc. For 11 SSc patients, a follow-up of 12 months was available and in these subjects a stabilisation of %pFVC and %DLCO was observed. To note that all SSc patients received at least one immunosuppressive drug. Among overall enrolled population, diarrhoea was the most common adverse event, followed by loss of appetite and nausea (52).

In the SENSCIS-ON extension study patients with SSc-ILD received long-term NTD treatment (32-36 months of median exposure). Among patients in the continued NTD group and those in the initiated NTD group, GI AEs were the most common, particularly diarrhoea (74–77%) leading to permanent discontinuation of NTD in 4.1% and 10.1% of patients, respectively. Weight loss was also observed over time, and serious AEs were reported in 38.6% of subjects in the continued group and in 38.5% in the initiated one. The authors reported a mean reduction in FVC of -189 mL in patients who continued NTD and of -126 mL in those who initiated the drug during the extension and similar patterns were observed regardless of concomitant MMF use, supporting the use of NTD to continue slowing the decline in LFTs (53).

In subgroup analyses of the SENSCIS trial, the authors aimed to compare the progression of SSc-ILD defined as the rate of FVC decline based on autoantibodies positivity in three populations: patients positive for ACA, patients positive for ARA and those with ACA, ARA and ATA negativity. The benefit of the treatment seemed to be more pronounced in ACA or ARA positive patients, while the decline of FVC appeared to be higher in the third population (ACA, ARA and ATA negativity). These data suggested a close monitorisation of the third population to a potentially higher risk of more rapid progression compared with the other two populations (54).

Overall, current evidence suggests that nintedanib provides sustained benefit in slowing SSc-ILD progression, with an acceptable safety profile, although treatment response appears to be influenced by concomitant immunosuppressive therapy and patient-specific clinical and serological features.

*Vasoactive therapies*

Vasoactive drugs represent a cornerstone in the management of SSc-related vasculopathy, particularly for RP and DUs. These agents aim to improve peripheral blood flow, reduce ischaemic episodes, and promote ulcer healing, thereby limiting vascular damage and tissue loss.

The multicentre retrospective case-control study of Iannone *et al*. compared the efficacy of selexipag with iloprost in healing DUs. The authors enrolled 96 patients, 32 treated with selexipag and 64 with iloprost reporting that selexipag was associated with markedly better outcomes, including higher ulcer healing rates, faster time to healing, and sustained reductions in ulcer recurrence and new lesion development over 24 months (55). Regarding refractory DUs a phase 3 pivotal study investigated if shock waves therapy may ameliorate this condition. The study included 30 SSc patients conventionally treated and 30 subjected to extracorporeal shock wave and after 8 weeks of treatment the authors reported a greater reduction of DUs number in this last population (56).

The inhibition of microsomal prostaglandin E2 synthase-1 (mPGES-1) leads to an increase of prostacyclin biosynthesis. Vipoglanstat is a selective inhibitor of mPGES-1 and its role in SSc-related RP has been studied in a multicentre phase 2 double-blind, placebo-controlled trial. Patients recruitment was temporarily paused during warmer months to limit seasonal influence on vascular outcomes, at the end of the enrolment 33 patients received vipoglanstat and 36 placebo. The primary endpoint was represented by the change in weekly Raynaud's attack frequency after four weeks and the two populations did not show significant difference both experiencing a reduction in attack frequency, as well as improvements in secondary clinical measures, including attack duration, pain severity, and Raynaud Condition Score (RCS), without differences between the two groups. Objective assessments of peripheral circulation, including thermographic analysis and cold challenge testing, also failed to demonstrate treatment-related advantages. Similarly, patient- and physician-reported global assessments improved modestly in both arms but did not differ significantly. No treatment-related serious safety concerns emerged in the active arm. Despite lacking clinical superiority over placebo, pharmacodynamic analyses demonstrated almost complete suppression of mPGES-1 activity, along with pronounced changes in downstream prostaglandin and thromboxane metabolite levels in the treatment arm (57).

All together these findings suggest that although novel vasoactive strategies are expanding the therapeutic landscape of SSc vasculopathy, their clini-

cal efficacy remains heterogeneous. In this context, the vipoglanstat trial seems to highlight the multifactorial nature of SSc vasculopathy by illustrating that robust pharmacological target inhibition does not necessarily translate into superior clinical outcomes.

*Others*

Chronic pain and fatigue are often associated to SSc and strongly influence patients' quality of life. Current available drugs have a limited efficacy, and non-pharmacological interventions are gaining growing attention. In this context a multicentre European trial was design o evaluate if a supervised combined exercise program could reduce pain and fatigue in patients with SSc patients also exploring its effects on physical function, fitness, and related patient-reported outcomes. In this study, a total of 170 participants were randomised to either exercise or usual care alone, with follow-up at 12 and 24 weeks. At 12 weeks the exercise group showed significant reductions in overall pain and RP-related symptoms, align with improvements in fatigue, quality of life, depressive symptoms and functional capacity compared with controls. Physical performance measures, including muscle strength and cardiorespiratory fitness, also improved. Some benefits (pain, depression, and certain functional outcomes) persisted at 24 weeks, however others, particularly fitness-related gains, were not fully maintained. Therefore, according to data from this study an exercise training appears safe and effective as an add-on therapy in SSc patients, enhancing general well-being (58). In SSc a high prevalence of psychological distress has been reported, with frequent depressive and anxiety symptoms, impaired stress coping abilities, and reduced overall well-being. Well-Being Therapy (WBT) is a short, structured psychotherapeutic approach derived from cognitive-behavioural principles that aims to emphasise the identification and reinforcement of positive emotional experiences and the interruption of thoughts that prematurely terminate states of well-being. A randomised controlled trial evaluated the efficacy of WBT in 16 patients compared to treatment as usual in 16 patients. the authors reported a reduction in emotional distress and an increase in psychological well-being in SSc patients treated with WBT. In addition, patients reported a reduction in mental pain and a lower perceived burden of illness, alongside improvements in daily functioning-related domains. All together these data suggested that interventions targeting psychological well-being may represent a promising complementary strategy in the management of SSc patients (59).

Hand involvement, due to RP, flexion contractures or inflammatory arthritis, strongly impact the quality of life of SSc patients and in this context occupational/physiotherapeutic therapy is mandatory as confirmed by the study of Okyar *et al*. The authors enrolled 22 patients receiving a three-week occupational therapy program and 20 patients for the control groups, demonstrating a significant improvements in hand function, including both grip and pinch strength, in the intervention population that also reported an improvement in tactile perception. Therefore, occupation therapy represents a key component in the management of scleroderma patients being associated with meaningful gains in hand performance and functional ability (60).

A phase 2, randomised, double-blind, placebo-controlled trial enrolled 67 SSc patients symptomatic for lower GI tract involvement and evaluated the efficacy and safety of faecal microbiota transplantation using an anaerobically cultivated human intestinal microbiome (ACHIM). Data from this study reported a general well toleration of the procedure (to note that one patient experienced a duodenal perforation during gastroscopy), however, the authors did not demonstrate a significance difference in gastrointestinal symptoms between the two groups (61).

CD19-targeting chimeric antigen receptor (CAR) T-cell therapy has recently been implemented for the management of severe autoimmune diseases such as systemic lupus erythematosus (SLE), SSc and idiopathic inflammatory myopathy (IIM) and the study of Hagen *et al*. aimed at evaluating its disease-specific AEs that remain poorly characterised. In this study a total of 39 patients (20 SLE, 13 SSc and 6 IIM) treated with CD19-directed CAR T-cell therapy and with a median follow-up of 11 months were investigated. 77% of these patients developed local immune effector cell-associated toxicity syndrome (LICATS), typically occurring within the first weeks after infusion during B-cell depletion. These manifestations were generally mild to moderate and self-limiting or responsive to short courses of GCs, with only a few severe cases reported. However, no events led to permanent complications (62).

Belumosudil is a selective inhibitor of ROCK2 (Rho-associated coiled-coil–containing protein kinase 2) that is involved in immune regulation and fibrosis. By blocking ROCK2 activity an immunological rebalancing is observed helping to restore immune homeostasis. In addition, ROCK2 inhibition, interfering with profibrotic signalling cascades driven by mediators such as TGF-β, seems to reduce fibroblast activation and extracellular matrix production. The efficacy of oral belumosudil in dcSSc with an early disease (≤5 years from first non-Raynaud symptom) and an active skin involvement, was investigated in a phase 2, multicentre, randomised, double-blind, placebo-controlled study. Most patients were receiving background immunosuppressive therapy, particularly MMF. The achievement of clinically meaningful improvement in the ACR CRISS score at week 24 was not met (primary endpoint) and no statistically significant differences were observed between treatment and placebo groups. Despite the lack of clear clinical efficacy, pharmacodynamic and exploratory analyses showed biological activity consistent with ROCK2 inhibition and histological assessment indicated a trend toward decreased dermal fibrosis over time in treated individuals (63).

Brentuximab vedotin is an antibody-drug conjugate against CD30 approved for lymphomas treatment and studied in a phase 2 open-label, single-arm, trial aiming on skin fibrosis. Data from this

trial, that included 9 patients completing the study and previously undergone unsuccessful immunosuppressive, suggested a benefit of brentuximab vedotin in skin involvement reporting a reduction of mRSS with the satisfaction of the primary endpoint. These results support the need for a large, placebo-controlled clinical trial to confirm these preliminary data (64).

Taken together, these findings support a multidisciplinary approach to SSc while highlighting the need for further validation of emerging therapies.

**Take home messages**

- Immunosuppressive therapies remain a cornerstone of SSc management as also reported by the recent guidelines for the treatment of ILD. Mycophenolate mofetil, rituximab and cyclophosphamide demonstrate consistent benefits in stabilising lung function and improving cutaneous involvement, particularly when used in combination or early in disease course (43, 45, 47).
- Antifibrotic therapy with nintedanib represents a key advance in SSc-ILD, effectively slowing the decline in lung function across different patient subsets, including those receiving background immunosuppression, although its use is limited by gastrointestinal adverse events (52, 53).
- Vasoactive treatments are essential in SSc-related vasculopathy (55), with prostacyclin pathway modulation and novel agents improving Raynaud's phenomenon and digital ulcers, while emerging interventional and pharmacological approaches continue to expand therapeutic options (56).
- Targeted and emerging immunomodulatory therapies are reshaping SSc treatment paradigms, including JAK inhibitors (49) and ROCK2 inhibition (63), this last one showed promising results in modulating inflammatory and fibrotic pathways, although robust clinical efficacy remains to be fully established.
- Multidisciplinary and adjunctive strategies are increasingly relevant in SSc management, including exercise-based rehabilitation, psychological interventions, and emerging biologic or cellular therapies (*e.g.* CAR T-cells) (58-60, 62). These approaches may represent a promising complementary strategy to improve SSc management, highlighting the need for a holistic approach to improve patient outcomes and quality of life.

**Patient-reported outcomes**

SSc is a very heterogeneous disease, and different patient-reported outcomes (PROs) have been proposed to capture the different features and the burden of the disease. At present, many PRO instruments used in SSc have been adapted from other disease contexts and therefore may not fully capture the specific and unique aspects of this condition.

The study of Colak *et al*. evaluated the EULAR Scleroderma Impact of Disease (ScleroID) questionnaire in a large cohort of patients with SSc with the specific purpose to assess its ability in capturing disease burden across different clinical subsets and to detect clinically meaningful change over time. A total of 271 patients with very early (68 patients), limited (139), and dcSSc (63) were analysed. ILD, small intestinal bacterial overgrowth (SIBO) and tendon friction rubs were more frequent among dcSSc. ScleroID scores varied significantly according to disease phenotype, with higher values observed in dcSSc compared with lc and very early disease. Moreover, distinct ScleroID domains reflected specific organ involvement, such as higher dyspnoea scores in patients with PAH, the highest median Raynaud score in patients presenting DUs and increased gastrointestinal scores in those with SIBO. These findings support the construct validity of the instrument in reflecting organ-specific disease manifestations. In addition, strong correlations were observed between ScleroID total and domain scores and established clinical measures and PROs, including HAQ-DI, CHFS, UCLA GIT 2.0, mRSS, FVC, and DLCO, indicating good convergent validity. Importantly, longitudinal analyses demonstrated that ScleroID scores were able to capture meaningful changes when aligned with minimal clinically important differences in key functional and GI outcome measures. Changes in ScleroID subdomains paralleled worsening or improvement in HAQ-DI, CHFS, and GI PROs, confirming its responsiveness to clinically relevant changes. Therefore, the ScleroID appears to be a comprehensive and sensitive instrument for assessing overall disease impact in SSc, capable of differentiating between disease subsets and reflecting organ involvements (65).

A previous study demonstrated the useful of the PASTUL (patient self-assessment of skin thickness in upper limb) questionnaire in the self-assessment of skin fibrosis and a subsequent study has been performed to validate this instrument across multiple UK scleroderma centres, particularly to evaluate it correlation with clinician assessment (mRSS) and with health-related quality of life (HRQoL) and other patient-reported outcomes (PROs). The authors enrolled 196 patients with SSc including both lc and dc subsets. Participants completed the PASTUL and other clinical and PRO measures, including mRSS, HAQ-DI, EQ5D5L, Leeds SSc QoL, and SSPRO. In a longitudinal subgroup, changes were also assessed over 6 and 12 months. PASTUL scores were different according to SSc subset, particularly they were higher in dcSSc compared with lcSSc and strongly correlated with upper limb mRSS. The questionnaire demonstrated good test-retest reliability and was considered feasible, quick to complete, and easy to understand by patients. Importantly, PASTUL scores correlated with HRQoL outcomes and functional impairment, in some cases showing stronger correlations than clinician-derived skin scores. However, sensitivity to change over time was limited, as changes in PASTUL did not consistently track longitudinal changes in mRSS. Overall, the study supported PASTUL as a feasible and patient-friendly tool for self-assessment of skin involvement in SSc although further refinement is needed to improve its responsiveness to change (66).

The assessment of psychological status in patients with SSc plays a central

role in disease management; however, currently available instruments are mainly focused on psychological distress or broad health-related quality of life and often lack proper validation. A study evaluated the WHO-5 Well-Being Index and the six-item version of Ryff's Psychological Well-Being Scale (PWB-6) that are two brief PROMs, in SSc patients. Data from this study reported that both instruments demonstrated acceptable to good measurement performance. Importantly, both tools were found to be brief, easy to administer, and generally well suited for use in clinical settings involving SSc patients. Therefore, the authors suggested that WHO-5 and PWB-6 can be considered useful instruments for capturing subjective psychological well-being in SSc, however, further research is needed to consolidate their role in both clinical practice and research (67).

### Take home messages

- Disease-specific patient-reported outcomes are essential in SSc, as newly developed tools such as ScleroID and PASTUL demonstrate improved ability to capture organ-specific disease burden and patient experience compared with generic instruments (65, 66).
- While emerging PRO instruments show good validity and feasibility, their responsiveness and longitudinal sensitivity remain variable, highlighting the need for further refinement to fully integrate them into routine clinical assessment and outcome measurement in SSc (67).

## Conclusions

This review summarises the most relevant advances in SSc research published in 2025, reflecting the ongoing efforts to unravel the complexity of this disease. Considerable progress has been made in understanding its pathogenic mechanisms, characterising clinical phenotypes and organ involvement, and expanding therapeutic options across different disease domains. However, SSc remains a highly heterogeneous condition in which early recognition and accurate stratification are still crucial unmet needs. The overarching goal is the implementation of precision medicine approaches, allowing treatment strategies to be tailored to individual disease trajectories. Achieving this objective will require earlier diagnosis, improved patient classification, and better prediction of disease course, ultimately aiming to enhance survival and quality of life in patients with SSc.

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