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SYSTEMIC SCLEROSIS: EPIDEMIOLOGY, CLASSIFICATION, PATHOGENESIS, ORGAN INVOLVEMENT, AND TREATMENT - A REVIEW OF PUBLISHED DATA

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Abstract. Systemic sclerosis (SSc, scleroderma) is a rare, chronic autoimmune connective-tissue disease characterized by the triad of microvascular injury, immune dysregulation with disease-specific autoantibodies, and progressive fibrosis of the skin and internal organs. This article reviews the current understanding of SSc on the basis of published epidemiological and clinical studies, with emphasis on real statistical data - prevalence, incidence, antibody frequencies, organ-involvement rates, survival, and treatment-trial outcomes. According to global meta-analyses, the prevalence of SSc is approximately 18-23 per 100,000 with a marked female predominance of about 4-8:1. The disease is divided into limited and diffuse cutaneous subsets, each associated with characteristic autoantibodies and patterns of organ involvement. Interstitial lung disease and pulmonary arterial hypertension are the leading causes of disease-related death. Recent randomized controlled trials (SENSCIS, focuSSced, SCOT) and the updated EULAR recommendations have substantially expanded the therapeutic options, including antifibrotic and biologic agents and autologous haematopoietic stem-cell transplantation.

Keywords: systemic sclerosis, scleroderma, autoantibodies, interstitial lung disease, pulmonary arterial hypertension, fibrosis, nintedanib, autologous stem-cell transplantation.

Introduction

Systemic sclerosis (SSc), commonly known as scleroderma, is a rare and complex autoimmune connective-tissue disease defined by three interacting pathological processes: injury and dysfunction of small blood vessels (vasculopathy), dysregulation of the innate and adaptive immune systems with the production of disease-specific autoantibodies, and progressive fibrosis of the skin and internal organs [2; 14]. Because of this multisystem fibrotic and vascular involvement, SSc carries the highest case-specific mortality among the systemic autoimmune rheumatic diseases.

The clinical course of SSc is highly heterogeneous, ranging from slowly progressive skin and vascular disease to rapidly fatal multi-organ failure. This heterogeneity, together with the overlap of early manifestations with other rheumatic conditions, makes early diagnosis, risk stratification, and individualized management particularly challenging. Over the past two decades, large international cohorts - notably the EULAR Scleroderma Trials and Research (EUSTAR) database - and a series of randomized controlled trials have considerably improved the evidence base. The aim of this article is to review the current understanding of SSc, drawing on previously published studies and their statistical data, with respect to epidemiology, classification, pathogenesis, autoantibody profiles, organ involvement and prognosis, and treatment.

Materials and methods

This work is an integrative (narrative) review based on a systematic analysis of the peer-reviewed literature published between 2003 and 2025, including classic earlier studies. The PubMed/MEDLINE, Annals of the Rheumatic Diseases, The Lancet and Lancet Respiratory

Medicine, New England Journal of Medicine, Rheumatology (Oxford), and Arthritis & Rheumatology databases were searched using the keywords “systemic sclerosis”, “scleroderma”, “epidemiology”, “autoantibodies”, “interstitial lung disease”, “pulmonary arterial hypertension”, and “treatment”. Priority was given to systematic reviews, meta-analyses, large registry and cohort analyses (in particular the EUSTAR cohort), and randomized controlled trials reporting quantitative outcomes such as prevalence, incidence, antibody frequencies, organ-involvement rates, survival, and trial endpoints.

Results

Definition, classification, and clinical subsets

According to the classification of LeRoy and colleagues, two principal cutaneous subsets are distinguished on the basis of the extent of skin involvement: limited cutaneous SSc (lcSSc), in which skin thickening is confined to areas distal to the elbows and knees and to the face, and diffuse cutaneous SSc (dcSSc), in which skin involvement extends to the proximal limbs and trunk [5]. The 2013 American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) classification criteria assign weighted scores to skin thickening, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud’s phenomenon, and SSc-specific autoantibodies; a total score of 9 or more classifies a patient as having SSc [1]. The two subsets differ markedly in their antibody associations, organ involvement, and prognosis (Table 1).

Table 1. Comparison of the limited and diffuse cutaneous subsets of systemic sclerosis

Feature	Limited cutaneous (lcSSc)	Diffuse cutaneous (dcSSc)
Extent of skin involvement	Distal to elbows/knees, plus face	Proximal limbs and trunk
Raynaud’s phenomenon	Often precedes skin changes by years	Onset close to skin changes (months)
Characteristic autoantibody	Anticentromere (ACA)	Anti-Scl-70; anti-RNA polymerase III
Typical major complication	Pulmonary arterial hypertension	Interstitial lung disease; renal crisis
Course and prognosis	Slower; comparatively better survival	Rapid; comparatively worse survival

Epidemiology

SSc is a rare disease whose reported frequency varies widely with geography and methodology. A global systematic review and meta-analysis estimated the worldwide prevalence at about 18.9 per 100,000 persons, corresponding to roughly 1.5 million affected people, with pooled estimates from other reviews of about 23 per 100,000 [3]. The reported incidence ranges from 0.77 per 100,000 person-years in the Netherlands to 5.6 per 100,000 person-years in the United States, and prevalence in Europe and North America from 7.2 to 33.9 per 100,000 [2; 3]. In a large United Kingdom cohort the annual incidence was 19.4 per million person-years and the prevalence 307 per million, with a peak age of onset of 55-69 years [4]. Like most autoimmune diseases, SSc shows a strong female predominance, with female-to-male ratios of about 3-8:1 (on average near 5:1) and

up to 14.5:1 in Japan; the diffuse subset, however, affects the sexes more equally [3; 4]. Selected estimates are summarized in Table 2.

Table 2. Selected epidemiological estimates for systemic sclerosis

Source / cohort	Prevalence	Incidence	Female : male
Global meta-analysis [3]	≈18.9/100,000	≈8.6/100,000 PY	≈5:1
United Kingdom, CPRD [4]	307/million	19.4/million PY	4.7:1
Europe / North America [2]	7.2–33.9/100,000	0.6–2.3/100,000 PY	3–8:1
Japan (highest ratio) [3]	—	—	up to 14.5:1

The wide variation in reported figures reflects genuine geographic and ethnic differences as well as methodological heterogeneity. Diffuse disease occurs more frequently and more severely in patients of African ancestry, the limited subset shows the strongest female predominance (up to about 10:1), and juvenile-onset SSc is very rare, with an incidence on the order of 0.3 per million children per year. Across populations the average age at onset lies in the fifth decade - close to 50 years in women and somewhat later in men - and both the diffuse subset and male sex are consistently associated with earlier organ involvement and reduced survival [2; 3].

Pathogenesis

The pathogenesis of SSc is conceptualized as the interplay of three processes. The earliest is vasculopathy: endothelial injury leads to Raynaud's phenomenon, intimal proliferation, progressive loss of capillaries, and impaired angiogenesis, producing chronic tissue ischaemia. The second is immune dysregulation, involving both innate and adaptive immunity, activation of T and B lymphocytes, production of disease-specific autoantibodies, and release of pro-fibrotic and pro-inflammatory mediators such as interleukin-6 and transforming growth factor-beta (TGF-β). The third and defining process is fibrosis: under the influence of TGF-β, platelet-derived growth factor (PDGF), and connective-tissue growth factor, fibroblasts differentiate into myofibroblasts that deposit excessive collagen and extracellular matrix in the skin and internal organs [2; 14]. These processes develop in genetically predisposed individuals (notably certain HLA class II alleles) and may be triggered by environmental factors such as silica exposure.

These three axes are interconnected and reinforce one another: ischaemia and oxidative stress amplify both immune activation and fibroblast stimulation, while immune mediators sustain the vascular and fibrotic processes. Vasculopathy is typically the earliest detectable abnormality - reflected in the nailfold capillary changes that can be visualized by capillaroscopy - and precedes overt fibrosis by months to years. This temporal sequence underlies the concept of "very early" SSc and the value of capillaroscopy and autoantibody testing for the early identification of patients at risk of progression.

Autoantibodies and their clinical associations

Antinuclear antibodies are detected in more than 90-95% of patients with SSc, and at least one of three mutually exclusive SSc-specific autoantibodies is found in up to 70% of cases [6]. These antibodies are not only diagnostic but also strongly prognostic, and they are incorporated as a scoring item in the 2013 ACR/EULAR criteria [1]. Anticentromere antibodies are associated with the limited subset and with pulmonary arterial hypertension; anti-topoisomerase I (anti-Scl-70) antibodies, present in 30-40% of diffuse cases, are associated with interstitial lung disease and extensive skin involvement; and anti-RNA polymerase III antibodies are markers of diffuse disease

and carry a high risk of scleroderma renal crisis (odds ratio about 7.8) as well as gastric antral vascular ectasia and an association with malignancy. The main antibodies and their associations are presented in Table 3.

Table 3. SSc-specific autoantibodies and their main clinical associations

Autoantibody	Main subset	Principal clinical association
Anticentromere (ACA)	Limited (lcSSc)	Pulmonary arterial hypertension; better survival
Anti-topoisomerase I (Scl-70)	Diffuse (dcSSc)	Interstitial lung disease; diffuse skin disease
Anti-RNA polymerase III	Diffuse (dcSSc)	Scleroderma renal crisis; GAVE; malignancy
Anti-Th/To	Limited (lcSSc)	PAH, ILD, renal - severe internal-organ disease
Anti-U3 RNP (fibrillarin)	Diffuse (dcSSc)	Pulmonary hypertension; cardiac; severe disease

Organ involvement and prognosis

SSc affects virtually every organ system. Cutaneous disease progresses through oedematous, indurative, and atrophic phases and may be accompanied by telangiectasia and calcinosis. Gastrointestinal involvement, present in up to 90% of patients, ranges from oesophageal reflux and dysmotility to gastric antral vascular ectasia and malabsorption. Cardiac involvement - myocardial fibrosis, conduction disturbances, and arrhythmias - is frequently clinically silent yet prognostically important, while musculoskeletal manifestations include arthralgia, tendon friction rubs, and myopathy.

Raynaud's phenomenon is almost universal (about 95% of patients) and digital ulcers are common. Gastrointestinal involvement, especially oesophageal dysmotility, affects the majority of patients, while musculoskeletal, cardiac, and renal manifestations contribute substantially to morbidity. Interstitial lung disease (ILD) is the most important organ complication: clinically relevant ILD is reported in roughly 16-47% of patients, occurring in about 60% of diffuse and 20% of limited cases, and it is the leading cause of SSc-related death. Pulmonary arterial hypertension (PAH) affects approximately 6-12% of patients and, historically, carried an annual mortality of around 30%; it remains a leading vascular cause of death. Scleroderma renal crisis, once a frequent fatal event, has been transformed by angiotensin-converting-enzyme (ACE) inhibitors.

Survival in SSc is well below that of the general population, with a standardized mortality ratio of about 4. In the United Kingdom cohort, survival at 1, 5, and 10 years was 94.2%, 80.0%, and 65.7%, respectively [4], while a EUSTAR-based Chinese cohort reported 1-, 3-, 5-, and 10-year survival of 97.0%, 94.6%, 91.1%, and 87.8% [analysis of EUSTAR data]. In the large EUSTAR analysis of causes of death, 55% of deaths were directly attributable to SSc; of these, 35% were due to ILD, 26% to PAH, and 26% to cardiac causes [7]. Poorer prognosis is associated with male sex, older age at onset, the diffuse subset, renal crisis, PAH, ILD, and anti-topoisomerase I or anti-U1 RNP antibodies. Importantly, the leading cause of SSc-related death has shifted over recent decades from renal crisis - controlled since the introduction of ACE inhibitors - to ILD and PAH [8].

Because internal-organ involvement is frequently asymptomatic in its early stages, regular screening is central to management: pulmonary function testing with measurement of the diffusing capacity and high-resolution computed tomography for interstitial lung disease, transthoracic echocardiography - with right-heart catheterization when indicated - for pulmonary arterial hypertension, and regular blood-pressure and renal monitoring for renal crisis. Early detection of these complications is the principal opportunity to modify the otherwise poor prognosis of the disease.

Treatment

Because SSc has no single curative therapy, management is organ-based and, in the updated 2023 EULAR recommendations, is organized into "therapeutic continuums" for fibrotic and vascular manifestations [13]. For skin fibrosis, methotrexate, mycophenolate mofetil, and rituximab are recommended, with tocilizumab at a lower evidence level. For SSc-ILD, mycophenolate, cyclophosphamide, rituximab, and the antifibrotic tyrosine-kinase inhibitor nintedanib carry the highest strength of evidence, with tocilizumab one level below. Vascular manifestations - Raynaud's phenomenon, digital ulcers, and PAH - are managed along a continuum that includes calcium-channel blockers, phosphodiesterase-5 inhibitors, endothelin-receptor antagonists, and prostacyclin analogues; upfront combination therapy is now recommended at the diagnosis of PAH, whereas anticoagulation with warfarin is explicitly discouraged. Scleroderma renal crisis is treated with ACE inhibitors. Key randomized trials underpinning these recommendations are summarized in Table 4.

Table 4. Selected landmark therapeutic trials in systemic sclerosis

Trial (agent)	Indication	Key result
SLS II (mycophenolate vs cyclophosphamide) [9]	SSc-ILD	Comparable FVC improvement; mycophenolate better tolerated
SENSCIS (nintedanib) [10]	SSc-ILD	Annual FVC decline reduced by 41.0 mL/year vs placebo (p=0.04)
focuSSced (tocilizumab) [11]	Early dcSSc / ILD	Preservation of lung function (FVC)
SCOT (autologous HSCT) [12]	Severe early dcSSc	Superior event-free and overall survival vs cyclophosphamide

Finally, high-intensity immunosuppression followed by autologous haematopoietic stem-cell transplantation (HSCT) has the strongest evidence among disease-modifying strategies, demonstrated in the ASSIST, ASTIS, and SCOT trials, and is recommended for selected patients with early severe diffuse disease and a poor prognosis, in the absence of advanced cardiorespiratory involvement [12; 13].

Discussion

The published data reviewed here confirm that SSc remains the rheumatic disease with the highest case-specific mortality, yet they also document substantial progress. The epidemiological picture is consistent across regions in its core features - rarity, marked female predominance, and peak onset in middle age - despite wide numerical variation attributable to differing case definitions and the impact of the 2013 ACR/EULAR criteria, which improved early case capture [1; 3]. The autoantibody-based framework has proven especially valuable, because the three SSc-specific

antibodies stratify patients into clinically meaningful phenotypes and allow targeted organ screening - for example, vigilance for renal crisis in anti-RNA polymerase III-positive patients and for ILD in anti-Scl-70-positive patients [6].

The most striking change is in therapy and in the causes of death. The control of scleroderma renal crisis by ACE inhibitors shifted the principal causes of mortality toward ILD and PAH [8], and the subsequent introduction of antifibrotic (nintedanib), biologic (tocilizumab, rituximab), and transplantation (HSCT) strategies has, for the first time, provided disease-modifying options for lung and skin fibrosis [10; 11; 12; 13]. Nevertheless, important challenges persist: there is still no cure, early diagnosis remains difficult, evidence for gastrointestinal and vascular immunosuppression is limited, and access to advanced therapies is uneven worldwide.

Looking ahead, research priorities include the validation of biomarkers for early diagnosis and for prediction of progression, the extension of immunosuppressive and antifibrotic strategies to gastrointestinal and vascular disease, and the refinement of patient selection for stem-cell transplantation. Precision-medicine approaches that combine autoantibody status, capillaroscopic findings, and molecular signatures are expected to enable earlier and more individualized intervention, which is the most promising route to further reducing the high mortality of the disease.

Limitations. This review is integrative rather than meta-analytic; the epidemiological figures are sensitive to differences in case ascertainment and study design, and antibody-frequency estimates depend on the assays used. The cited cohort and trial results should therefore be interpreted within their specific populations and methodologies.

Conclusion

1. Systemic sclerosis is a rare autoimmune disease defined by the triad of vasculopathy, immune dysregulation, and fibrosis; it has a marked female predominance (about 4-8:1) and a prevalence of roughly 18-23 per 100,000.
2. Two cutaneous subsets - limited and diffuse - together with the three SSc-specific autoantibodies (anticentromere, anti-Scl-70, and anti-RNA polymerase III) define clinically meaningful phenotypes that guide prognosis and organ screening.
3. Interstitial lung disease and pulmonary arterial hypertension are the leading causes of disease-related death; risk stratification by antibody profile and systematic organ screening are therefore essential.
4. Modern, organ-targeted treatment - including mycophenolate, nintedanib, tocilizumab, rituximab, ACE inhibitors, combination therapy for PAH, and autologous stem-cell transplantation for selected severe cases - has improved outcomes, although early diagnosis and individualized management remain decisive.

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