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# CLINICAL, GENETIC AND PROGNOSTIC FACTORS IN SYSTEMIC SCLERODERMA

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Systemic sclerosis, a chronic autoimmune connective tissue disease, is marked by skin thickening, Raynaud's phenomenon, visceral organ damage, and musculoskeletal involvement, presenting a significant challenge in rheumatology and immunology [7,8]. The pathogenesis of systemic sclerosis involves intricate interactions between the immune system, vasculature, and connective tissue, necessitating simultaneous dysfunction in immune tolerance, endothelial physiology, and extracellular matrix turnover [1,5]. The varied clinical presentation of systemic sclerosis, ranging from limited cutaneous involvement to diffuse systemic manifestations, underscores the disease's heterogeneous nature and the need for personalized treatment strategies [2,9]. Despite the disease's relatively low incidence, approximately 13 per 1 million people per year, and a prevalence of about 200 per 1 million, its impact on patient morbidity and mortality is substantial, necessitating ongoing research into its underlying mechanisms and therapeutic interventions [10,12]. The disease's complexity is further compounded by the diverse array of autoantibodies associated with systemic sclerosis, including anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III antibodies, which correlate with distinct clinical phenotypes and disease outcomes.

Systemic sclerosis diagnosis can be straightforward in patients exhibiting classic manifestations like Raynaud syndrome, dysphagia, and skin tightening, but it can be clinically challenging to diagnose when these symptoms do not come together, so confirmatory laboratory tests can help, but their absence does not exclude the diagnosis. Systemic sclerosis is a heterogeneous disease with varied clinical manifestations. The 2013 American College of Rheumatology and European League Against Rheumatism classification criteria for systemic sclerosis incorporates various clinical and serologic parameters to aid in diagnosis and classification [3,5]. These criteria assign weighted scores to clinical features such as skin thickening, Raynaud's phenomenon, and autoantibody profiles, improving diagnostic accuracy and facilitating earlier diagnosis. The presence of certain autoantibodies, such as anti-topoisomerase I (anti-Scl-70), anti-centromere, and

anti-RNA polymerase III antibodies, is associated with distinct clinical subsets and disease outcomes [1,4]. Early diagnosis and risk stratification are crucial for optimizing treatment strategies and improving patient outcomes in systemic sclerosis. Recent data suggest that "scleromyositis", a novel disease subset, should be recognized within the systemic sclerosis and autoimmune myositis spectrum [3,6]. Classic SSc-specific autoantibodies include anticentromere, -topoisomerase I, -RNA polymerase III, -Th/ To and -U3RNP, whereas SSc-overlap aAbs include anti-U1RNP, -PM-Scl and -Ku [7,11]. Anti-PM/Scl antibodies are detected in approximately 2% of SSc patients, but their presence is more common in SSc with myositis overlap.

Systemic sclerosis is considered a relatively rare disease, yet its impact on patient morbidity and mortality is substantial. Current epidemiological data indicate an approximate incidence of 13 new cases per 1 million people per year, with a prevalence estimated at about 200 per 1 million people [2,9]. The disease's diverse clinical presentation, which ranges from limited cutaneous involvement to diffuse systemic manifestations, underscores its heterogeneous nature and highlights the need for personalized treatment strategies [10,12]. Early diagnosis and risk stratification are crucial for optimizing patient outcomes in SSc [4,9].

Genetic factors contribute significantly to systemic sclerosis susceptibility, with genome-wide association studies identifying multiple risk loci associated with disease development. These genetic variants implicate immune-related genes and pathways, providing insights into the immunopathogenesis of systemic sclerosis. However, genetic predisposition alone is insufficient to trigger disease onset, highlighting the importance of environmental factors in systemic sclerosis pathogenesis. Environmental exposures, such as silica dust, organic solvents, and certain viral infections, have been implicated as potential triggers for systemic sclerosis in genetically susceptible individuals. These environmental factors may activate the immune system, promote inflammation, and initiate the fibrotic processes characteristic of systemic sclerosis [3,5]. Further research is needed to fully elucidate the complex interplay between genetic predisposition and environmental factors in systemic sclerosis pathogenesis.

Genetic factors significantly contribute to an individual's susceptibility to systemic sclerosis. Genome-wide association studies have been instrumental in identifying multiple risk loci linked to disease development [6,11]. These genetic variants often involve immune-related genes and pathways, providing valuable insights into the immunopathogenesis of SSc [3,4]. However, genetic predisposition alone is not sufficient to trigger disease onset, emphasizing the critical role of environmental factors in the disease's overall pathogenesis. Recent investigations,

as indicated within your document, have begun to pinpoint specific genetic contributions to SSc. For example, genes from the Integrin family, such as *ITGA5*, *ITGB2*, and *ITGB5*, have been identified as participants in the pathological processes of systemic sclerosis [8,12]. This suggests their involvement in how the disease manifests, although further research is needed to fully elucidate their precise roles.

Systemic sclerosis exhibits a wide spectrum of clinical manifestations, affecting various organ systems and resulting in diverse clinical phenotypes. The extent and severity of skin involvement, the presence of specific autoantibodies, and the pattern of organ involvement define distinct clinical subsets of systemic sclerosis. Limited cutaneous systemic sclerosis, characterized by skin thickening limited to the distal extremities and face, is typically associated with anti-centromere antibodies and a lower risk of severe organ involvement. Diffuse cutaneous systemic sclerosis, characterized by widespread skin thickening involving the trunk and proximal extremities, is associated with anti-topoisomerase I and anti-RNA polymerase III antibodies and a higher risk of pulmonary fibrosis and renal crisis. Interstitial lung disease is a frequent and severe complication, occurring in a large percentage of systemic sclerosis patients, becoming the major cause of mortality in this population [10,13]. The advent of high-resolution computed tomography has improved the detection and monitoring of SSc-ILD [12,15]. Cardiac involvement, including myocardial fibrosis, pericarditis, and pulmonary hypertension, is a significant cause of morbidity and mortality in systemic sclerosis. Juvenile systemic sclerosis is a rare multisystem autoimmune disorder characterized by vasculopathy and multiorgan fibrosis. The Integrin family genes, like ITGA5, ITGB2, and ITGB5, have been found to participate in the pathological processes of systemic sclerosis, though more research is needed [3,7].

The pathogenesis of systemic sclerosis involves a complex interplay of immune dysregulation, vascular damage, and fibroblast activation, leading to excessive collagen deposition and tissue fibrosis. The activation of immune cells, such as T cells, B cells, and macrophages, contributes to the inflammatory milieu in systemic sclerosis, promoting the release of pro-inflammatory cytokines and chemokines that perpetuate the fibrotic process [2,8]. Transforming growth factor-β plays a pivotal role in the process of fibroproliferation, and multiple cytokines have been implicated, such as connective tissue growth factor, interleukin, and chemokines [1,8]. Aberrant activation of fibroblasts, the primary collagen-producing cells in the skin and internal organs, results in excessive deposition of extracellular matrix components, leading to tissue fibrosis and organ dysfunction. Oxidative stress has been implicated in the pathogenesis of systemic sclerosis, with

increased production of reactive oxygen species and impaired antioxidant defenses contributing to fibroblast activation and tissue damage [1,14]. Epigenetic modifications, such as DNA methylation and histone acetylation, have been implicated in the regulation of gene expression in systemic sclerosis fibroblasts, contributing to the persistent fibrotic phenotype. Macrophages are important cells that perform innate and adaptive immune functions [7,11]. However, failure to resolve macrophage activation can lead to chronic inflammation and fibrosis.

Several clinical and laboratory parameters have been identified as important prognostic factors in systemic sclerosis, allowing for risk stratification and prediction of disease outcomes. The extent of skin involvement, the presence of specific autoantibodies, and the pattern of organ involvement are important predictors of disease progression and survival in systemic sclerosis [9,15]. Patients with diffuse cutaneous systemic sclerosis, anti-topoisomerase I antibodies, and pulmonary fibrosis have a worse prognosis compared to those with limited cutaneous systemic sclerosis, anti-centromere antibodies, and no organ involvement. Elevated levels of certain biomarkers, such as C-reactive protein and erythrocyte sedimentation rate, are associated with increased disease activity and a higher risk of organ involvement. The identification of reliable prognostic factors is crucial for guiding treatment decisions and optimizing patient management in systemic sclerosis.

Current therapeutic approaches for systemic sclerosis focus on managing symptoms, suppressing inflammation, and preventing or slowing down disease progression. Immunosuppressive agents, such as methotrexate and mycophenolate mofetil, are commonly used to reduce inflammation and prevent further organ damage in systemic sclerosis. Cyclophosphamide and rituximab are used in some instances [7,13]. The paradigm that fibrosis represents an irreversible change of organ architecture has been overthrown in both preclinical and clinical research [10,14]. Targeting Interleukin-10 may have potential as an anti-fibrotic therapy due to its anti-inflammatory properties [11,15]. Novel therapeutic strategies targeting specific molecular pathways involved in fibrosis, such as transforming growth factor-β signaling and fibroblast activation, are under development and hold promise for improving outcomes in systemic sclerosis. The advent of antifibrotic medications, initially studied and approved for the treatment of idiopathic pulmonary fibrosis, has opened new avenues for the treatment of systemic sclerosis-associated interstitial lung disease [3,14]. Therapeutic plasma exchange has been explored as a treatment strategy based on the idea that removing circulating factors like autoantibodies or immune complexes could improve symptoms [5,13]. CD19 CAR T-cell therapy has emerged as a potential strategy for

resetting aberrant autoimmunity in systemic sclerosis through deep depletion of B cells [8,12].

Real-world data confirm the efficacy and safety of nintedanib in treating SSc-ILD, particularly in early-stage disease with at least 10% lung fibrosis on HRCT [3,11]. The treatment of connective tissue disease-related interstitial lung diseases is difficult because there aren't many proven effective treatments [6,12].

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