Prognostic factors in systemic sclerosis

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ABSTRACT

Systemic sclerosis is a chronic disease involving the connective tissue of the skin and internal organs. It is characterised by disorders of peripheral microcirculation, immune dysregulation, and deposition of collagen fibres and other substances in connective tissue. The most common organ complications in systemic sclerosis include interstitial lung disease, pulmonary arterial hypertension, renal tubular hypertrophy, and arthritis. Imaging findings often precede clinical symptoms, so all patients should be screened as soon as possible, preferably in the asymptomatic phase of the disease. Treatment options for systemic sclerosis include immunomodulatory therapies as well as therapeutic modalities targeting vascular mechanics and connective tissue fibrosis. Efforts are underway to discover new, more sensitive and specific prognostic factors that would help to personalize therapies and thus improve the final treatment outcomes. Identified biomarkers would accelerate the implementation of appropriate treatments, delaying the progression of irreversible complications and decreasing mortality rates in patients.

Key words: systemic sclerosis, SSc, risk factors, pathogenesis.

INTRODUCTION

Systemic sclerosis (SSc, systemic scleroderma) is a heterogeneous chronic disease involving the connective tissue of the skin and internal organs. It has a varied course characterised by alternating phases of remission and exacerbation. SSc is more commonly diagnosed in women than in men, and the peak age of onset is between the third and fifth decades of life [1]. Systemic sclerosis has been divided into two main subtypes: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc), according to the distribution of skin involvement. lcSSc is characterised by skin fibrosis of the fingers (sclerodactyly), face and neck, and extremities distal to the elbows and/or knees. The course of lcSSc is usually slow, and the overall prognosis is fairly good. In contrast, dcSSc is characterised by a more dynamic course, with early involvement of internal organs. Skin thickening predominantly affects the trunk and areas proximal to the elbows or knees [2].

The diagnosis of systemic sclerosis relies primarily on clinical symptoms and follows the classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2013. The criteria used in the diagnostic work-up of systemic sclerosis include skin thickening of the fingers extending proximal to the metacarpophalangeal joints, calcinosis, telangiectasias, pulmonary arterial hypertension and/or interstitial lung disease, and the presence of SSc-related autoantibodies (anti-centromere, anti-topoisomerase I (anti-Scl-70), and anti-RNA polymerase III antibodies) [3]. Systemic sclerosis can be diagnosed if the sum of points attributed to respective disease symptoms is nine or more. The highest number of points, nine, has been assigned to skin sclerosis. Thus, meeting just one criterion is sufficient for diagnosis. Other charac-

teristics of systemic sclerosis include progressive fibrosis of the skin and changes in internal organs. The cardiovascular, respiratory, renal, osteoarticular, and central nervous systems are most commonly affected.

PROGNOSTIC FACTORS IN SYSTEMIC SCLEROSIS

Prognostic assessment is an important factor in selecting an appropriate treatment approach. Continuous efforts are being made to identify new, more sensitive and specific prognostic factors that would help to personalize therapies and thus improve the final treatment outcomes. The main adverse prognostic factors in systemic sclerosis encompass age, clinical presentation, disease stage, and the presence of specific antibodies in the blood serum.

CLINICAL PROGNOSTIC FACTORS

Gender and ethnicity appear to be important determinants of the development of systemic sclerosis. While most studies have found a higher prevalence of SSc in women, the mortality rate is higher in men [4]. The prevalence is also higher among black populations [5]. Systemic sclerosis can occur at any age, but most commonly develops between the third and fifth decades of life [1]. Studies have found differences in prognosis depending on the patient's age at diagnosis. Older age is a negative prognostic factor, irrespective of sex and race [6]. Internal organ involvement and the presence of symptoms including rapid, generalised skin involvement or the presence of joint contractures at the onset of the disease also hold prognostic significance [7].

ENVIRONMENTAL FACTORS

Several environmental factors have been found to contribute to the development of SSc symptoms, including epoxy resins, asbestos, silica and silicone, pesticides, smoking, and certain medications, like oral contraceptives and hormone replacement therapy [8, 9]. The mechanism underlying interactions between environmental factors and the immune system is not fully understood. Hypotheses include immune system activation and molecular mimicry. Exposure to environmental factors may induce oxidative stress and cause direct damage to endogenous proteins and DNA, leading to the activation of genes implicated in the development of SSc. Research has shown that, with regard to the clinical manifestations, myopathy and pigmentary changes are more prevalent in patients with previous exposure to environmental factors [10].

PROGNOSTIC FACTORS OF ORGAN COMPLICATIONS

Respiratory system

Interstitial lung disease (ILD) is the most common pulmonary manifestation and the primary cause of mortality in patients with systemic sclerosis [11]. It is associated with pulmonary fibrosis and the development of vascular alterations which are known to lead to pulmonary arterial hypertension (PAH), among other effects. Early ILD is often clinically silent, with initial symptoms including fatigue, exertional dyspnoea, dry cough, and disrupted sleep patterns. Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is diagnosed and monitored for progression with diagnostic imaging techniques such as high-resolution chest computed tomography (HRCT) or pulmonary function tests (PFTs).

HRCT is a diagnostic modality used in the assessment of conditions affecting internal organs, including the respiratory and cardiovascular systems. It provides a more precise cross-sectional view of the lungs compared to a regular CT scan, thus allowing earlier detection of organ abnormalities. Because of its superior specificity compared to traditional imaging methods, HRCT is considered the gold standard for diagnosing SSc-ILD. The most typical manifestation of systemic sclerosis on HRCT scans is non-specific interstitial pneumonia (NSIP), characterised by symmetrical focal areas of ground-glass opacities, reticular lesions, and in advanced disease stages, reduced lung lobe volume [12]. Other common changes include dilatation of the pulmonary trunk and right ventricular hypertrophy, indicating progression to pulmonary arterial hypertension (PAH) [13].

Prognostic factors predicting the progression of SSc-ILD include low initial forced vital capacity (FVC), extensive interstitial lung disease seen on HRCT, and the presence of autoantibodies against topoisomerase I (anti-Scl-70), Pm/Scl, anti-U3RNP and anti-Th/To [14].

Cardiovascular system

Cardiac involvement, which develops as a direct consequence of systemic sclerosis, correlates with elevated mortality rates in patients. The most prevalent cardiac complications in patients with SSc are myocarditis, fibrosis of the conduction system, and pericardial and valvular diseases. One of the most severe complications of SSc is PAH, developing in 10–15% of patients [15]. The symptoms of PAH often manifest late, which contributes to unfavourable treatment outcomes [16]. At the onset, patients might experience symptoms linked to declining exercise tol-

erance, such as breathlessness, weakness, and chest pain. Advanced PAH is associated with increased abdominal girth and swelling in the lower extremities. The gold standard in the diagnosis of PAH is cardiac catheterisation, which allows for the measurement of pulmonary artery pressure (PAP). Pulmonary arterial hypertension is defined as a mean PAP ≥ 25 mm Hg at rest, > 30 mm Hg during exercise, or systolic pulmonary arterial pressure > 40 mm Hg [17]. Other useful diagnostic methods in PAH include computed tomography, which can reveal enlargement of the pulmonary arteries, right atrium and ventricle, and right ventricular hypertrophy; and electrocardiogram, where right ventricular hypertrophy is manifested by a peaked P wave with amplitude ≥ 2.5 mm in leads II, III and aVF (P pulmonale) [18]. Furthermore, the presence of anti-TOPO-I and anti-U3RNP antibodies and elevated levels of B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin T (HS-cTnT) may indicate potential cardiac involvement and correlate with disease severity, which positions them as promising screening parameters for the development of PAH in patients with systemic sclerosis [19, 20].

Urinary system

The primary renal complication of systemic sclerosis is rapidly progressive renal failure, referred to as scleroderma renal crisis (SRC), affecting 10% of SSc patients [21]. Symptoms of SRC include hypertension-associated headaches, heart failure, pericardial effusion, and acute kidney injury. The main prognostic factors for the development of SRC in patients with systemic sclerosis comprise generalised skin involvement, glucocorticosteroid use, newly diagnosed anaemia, and the presence of serum antibodies directed against RNA polymerase III, topoisomerase I, U3RNP, and Th/To [22, 23].

CHANGES IN CAPILLAROSCOPY

Capillaroscopy is a non-invasive technique used to assess capillary architecture and microcirculation, and thus determine disease progression. Capillaroscopy alterations have been incorporated into the most recent diagnostic criteria for systemic sclerosis. Capillaroscopic abnormalities in SSc patients can precede the onset of organ lesions by years or even decades, particularly when Raynaud's phenomenon is present. Capillaroscopic pattern in systemic sclerosis comprises giant capillaries, haemorrhages, avascular regions, capillary derangement, and neoangiogenic capillaries [24].

AUTOANTIBODIES IN SYSTEMIC SCLEROSIS

Autoantibodies are present in nearly all patients with systemic sclerosis. Since antinuclear antibodies (ANA) are the most frequently detected (90–95% of cases), they are routinely evaluated as diagnostic and prognostic biomarkers despite their relatively low specificity. ANA subtypes facilitate the classification of most patients with SSc, which is why they are included in the latest 2013ACR/EULAR Classification Criteria.

Autoantibodies associated with systemic sclerosis include anti-centromere antibodies (ACA), anti-topoisomerase I autoantibodies (ATA, Topo I, Scl-70), and anti-RNA polymerase III antibodies (RNAP). A new classification scheme for systemic sclerosis, proposed by Nihtyanov *et al.*, encompasses seven antibody groups: ACA lcSSc, ATA lcSSc, ATA dcSSc, anti-RNAP, anti-U3RNP, other lcSSc antibodies, and other dcSSc antibodies [25]. Nuclear antigens, such as Th/To (7–2 RNP, 8–2 RNP), SS-A and SS-B, anti-PDGFR, anti-BICD2, NOR 90, Ku, RuvBL1/2 and PM/Scl, are less commonly found [26].

The type of antibodies detected in the serum can help predict the subtype of systemic sclerosis and aid in assessing the prognosis. ACA, Th/To, and Ku antibodies are predominantly linked to limited systemic sclerosis, whereas Scl70 and RNA Pol III antibodies are associated with diffuse systemic sclerosis. Also, patients with Scl70, RNA Pol III and U1RNP have significantly reduced survival rates compared with ACA (+) patients [27].

In approximately 5% of individuals with systemic sclerosis, test results are negative for serum antinuclear antibodies, but their absence does not rule out the diagnosis. In this patient group, the disease tends to be more prevalent among men, exhibiting a more severe course and more frequently affecting the lower gastrointestinal tract [28].

Anti-topoisomerase I antibodies

Anti-topoisomerase I antibodies (ATA, anti-Scl-70, anti-TOPO-I) occur in 22–40% of patients with systemic sclerosis and are highly specific for the disease. They tend to be more prevalent in diffuse SSc (dcSSc), and their presence is associated with a more severe disease course and the development of organ complications, particularly the progression of interstitial lung disease (ILD). ATA may also correlate with oral manifestations like thinning of the rubor labiorum, xerostomia, and paradontopathy, as well as flexion contractures observed in the metacarpophalangeal and proximal interphalangeal joints [29, 30].

Anti-centromere antibodies

Anti-centromere antibodies (ACA) are commonly detected in limited systemic sclerosis. They have

a higher detection rate in Hispanic and Caucasian patients compared to individuals of African-American and Asian ethnicities [31]. Their presence increases the risk of pulmonary fibrosis and pulmonary hypertension, but in most cases it is associated with a more favourable disease course. Furthermore, individuals who are ACA(+) are more likely to have vascular irregularities identified early in capillaroscopy, which may predispose them to finger ulceration [32, 33].

Anti-RNA polymerase III antibodies

Anti-RNA polymerase III antibodies (ARA, RNAP) are found in approximately 12% of patients with systemic sclerosis. They are mainly associated with the diffuse form of the disease (dcSSc) and rapidly progressive thickening of the skin. The prevalence of ARA is greater among European patients and lower among Asian patients [31]. The presence of these antibodies is linked to an elevated risk of heart failure and scleroderma renal crisis, as well as more frequent involvement of the musculoskeletal system [33].

Anti-fibrillarin antibodies

Antibodies against fibrillarin are present in the serum of approximately 4% of patients with systemic sclerosis. Their presence is linked to earlier disease onset and worse prognosis [34]. Anti-U3RNP antibodies are more commonly detected in males and individuals of African-American ethnicity [35]. Among anti-U3RNP(+) patients, there is an increased prevalence of skeletal muscle involvement and pulmonary arterial hypertension, which represents the primary cause of mortality [36]. The presence of anti-U11/U12 RNP antibodies is associated with a higher incidence of Raynaud's phenomenon, gastrointestinal manifestations, and pulmonary fibrosis. Also, U1RNP antibodies in the serum has been found to be significantly correlated with pulmonary arterial hypertension [36, 37].

Anti-PM/Scl antibodies

An association has been reported between the presence of anti-PM/Scl antibodies and a higher incidence of inflammatory myopathy, as well as longer progression-free survival time in patients with systemic sclerosis [38].

Anti-ANP32A antibodies

Antibodies directed against nuclear phosphoprotein 32A (anti-ANP32A) have been found in roughly 4% of individuals diagnosed with systemic sclerosis. Patients testing positive for anti-ANP32A antibodies might be more prone to developing pulmonary arterial hypertension and less likely to experience severe Raynaud's phenomenon [39].

NON-CODING RNAS (NCRNAS)

Non-coding RNAs (ncRNAs) are among the most commonly studied epigenetic mechanisms. ncRNAs have the form of chains circulating in the blood, varying in length from 20 to 200 nucleotides. They play a pivotal role in cellular function at the molecular level by regulating gene expression post-transcriptionally. More than 90% of the human genome consists of ncRNA, which can be divided into several types: short interfering RNA (siRNA), circular RNA (circRNA), medium-chain micro RNA (miRNA) and long non-coding RNA (lncRNA). They serve as promising candidates for diagnostic and prognostic biomarkers, and also hold potential as therapeutic targets in various autoimmune conditions, including systemic sclerosis. In view of their high stability, tissue specificity, and close associations with the pathomechanisms underlying various diseases, an increasing amount of research is focusing on lncRNAs as novel biomarkers of tissue damage in the diagnosis and prognosis of systemic sclerosis.

Recent studies have confirmed positive correlations between serum miRNA expression levels and the diagnosis of systemic sclerosis. Among other findings, reduced levels of miRNA-181a and miR-138, and overexpression of miR-126, miR-139-5p, miR-618, miR-132, miR-143, miR-145 and miR-155 have been detected in the serum of patients [40–44]. Also, a link has been shown between the pulmonary complications of SSc and the expression of individual miRNAs. Furthermore, there is a reported correlation between miR-20a-5p and miR-203a-3p expression levels and the incidence of PAH in patients with ACA(+) lcSSc [41]. Patients with systemic sclerosis and FVC ≤ 70% were found to show decreased levels of miR-143 in comparison to patients having normal FVC levels. Also, miR-132 expression was shown to be higher in the dcSSc subgroup with detected active lung lesions compared to dcSSc patients with fibrotic lesions [43].

EPIGENETICS AND IMMUNE CELLS

Epigenetics involves studying changes in gene expression that occur without modifications in their underlying nucleotide sequences. In patients with systemic sclerosis, epigenetic alterations lead to an imbalance in the differentiation and function of T cells. Cytotoxic CD4+ T cells (CD4+ CTL) and CD8+ T cells (CD8+ CTL) are involved in the formation of inflammatory infiltrates in the skin, primarily consisting of T cells. By employing antibodies that detect cleaved caspase-3 (cCasp-3) in tissues, researchers identified a build-up of apoptotic cells alongside the accumulation of both CD8+ CTL and CD4+ CTL.

This observation indicates the potential involvement of CTL in the fibrosis process through induction of cellular apoptosis and release of profibrotic cytokines [45]. Therefore, it is likely that interventions targeting cytotoxic T cells early in the course of the disease have the potential to halt the progression of the condition.

INTERLEUKIN-6

Interleukin-6 (IL-6) contributes to the pathogenesis of systemic sclerosis. Tocilizumab, a monoclonal antibody directed against the interleukin IL-6 receptor, was the first biologic drug approved by the FDA for use in patients with interstitial lung disease associated with systemic sclerosis [46, 47].

PLASMACYTOID DENDRITIC CELLS

Plasmacytoid dendritic cells (pDCs) show abnormal TLR8 signalling in patients with systemic sclerosis and release more IFN-α after TLR stimulation compared to healthy cells [48, 49]. Additionally, pDCs secrete significant quantities of chemokine ligand 4 (CXCL4), while elevated levels of circulating CXCL4 correlate with the severity of skin fibrosis and pulmonary fibrosis [50].

G PROTEIN-COUPLED RECEPTORS (GPCRS)

G protein-coupled receptors (GPCRs) represent the largest family of membrane receptors in the human genome. Their mechanism involves coupling to G protein for the purpose of modulating intracellular signalling pathways, and leading to the activation of cellular responses. The GPCR family encompasses various receptors, including angiotensin II receptor subtype 1 (AT1R) and endothelin type A receptor (ETAR) which are expressed in fibroblasts, pulmonary endothelial cells, skin cells, and immune cells, among other cell types. Patients with systemic sclerosis showed increased AT1R and ETAR expression in these cells, which correlated with a more severe disease course [51]. Long-term treatment with angiotensin receptor blockers was also found to be linked to a decrease in adverse effects and reduced mortality rates in patients diagnosed with systemic sclerosis [52].

CONCLUSIONS

The understanding of prognostic factors in systemic sclerosis is consistently expanding. Laboratory diagnostic factors demonstrate a potential to establish a diagnosis faster and using less invasive diagnostic methods compared to clinical prognostic factors. Efforts are also underway to identify new, highly sensitive and specific biomarkers specific to SSc. Such biomarkers would enable personalised therapy, thereby improving treatment outcomes and the assessment of risk of irreversible complications. Furthermore, established biomarkers would facilitate more effective disease monitoring and contribute to lowering the mortality rates in SSc patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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