# Systemic sclerosis: can we identify patients at risk?

Leeuwen, N.M. van

# General introduction and outline

# SYSTEMIC SCLEROSIS

*A complex and heterogeneous auto-immune disease*

Systemic Sclerosis (SSc) is a relatively rare disease. The prevalence in the Netherlands has been estimated at 8.9 per 100.000 inhabitants using the American College of Rheumatology (ACR) preliminary criteria and LeRoy's criteria [1]. The diagnosis of SSc is generally suggested by the presence of Raynaud's Phenomenon (RP) consecutively followed by skin thickening associated with the presence of additional organ manifestations, microvascular abnormalities and SSc specific autoantibodies [2]. RP is present in 95% of the patients, it precedes other symptoms by years, and is classically viewed as reversible vasospasm due to functional changes in digital arteries of the hands and feet [3]. After the skin, gastro-intestinal (GI) complaints are most prevalent in SSc [4]. More life threatening organ complications include interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), and cardiac involvement [5, 6]. Compared to the general population, but also to patients with other rheumatic diseases or chronic conditions, health-related quality of life (HRQoL) is significantly more affected in SSc patients. Optimal management of SSc is challenging due to severity, heterogeneity and complexity of the disease. SSc can be progressive and many of the disease features can aggravate over time. Therefore annual screening of SSc patients for disease severity and/or progression is advocated using standardized programs with a multidisciplinary approach [7]. Here, patients are seen on a yearly basis by a multidisciplinary team including a rheumatologist, pulmonologist, specialized rheumatology nurse, physical therapist, and if needed, a dietician, occupational therapist, cardiologist, gastroenterologist or dermatologist. Even with this approach it remains difficult to accurately identify the trajectory of the disease in the individual patient. The first five years after diagnosis are most critical in determining the individual patient's prognosis [8]. With the introduction of new diagnostic guidelines in 2013, the diagnosis is more frequently set in an early phase [9]. The ACR/European League against Rheumatism (EULAR) 2013 classification criteria for SSc reflect the need to create an earlier treatment window, based on better understanding of the pathogenesis. These criteria recognize the importance of nailfold capillaroscopy (NC) to identify the degree of vasculopathy in early diagnosis, and the role of specific SSc autoantibodies in clinical manifestations and disease prognosis. However, even with the use of the ACR/EULAR 2013 criteria patients with very early or mild SSc can be missed. To detect patients with very early disease, the EULAR scleroderma Trials and Research group (EUSTAR) developed the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria [10, 11]. Unfortunately, earlier diagnosis has not led to improvements in determining the prognosis in the individual patient due to lack of accurate prognostic markers [12] and tailormade assessment and treatment of the individual SSc patient remains challenging. In addition, with the shift towards early recognition it is important and helpful to know how early diagnosis affects patients, as illness perceptions directly influence illness behaviour [13, 14].

**The ACR/EULAR criteria for the classification of SSc***

| Item | Sub-item(s) | Weight/score # |
|---|---|---|
| Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints | - | 9 |
| Skin thickening of the fingers (only count the higher score) | Puffy fingers<br>Sclerodactyly | 2 4 |
| Fingertip lesions (only count the higher score) | Digital tip ulcers Fingertip pitting scars | 2 3 |
| Telangiectasia | - | 2 |
| Abnormal nailfold capillaries | - | 2 |
| Pulmonary arterial hypertension or interstitial lung disease | - | 2 |
| Raynaud Phenomenon | - | 3 |
| Scleroderma related autoantibodies | Anti-centromere Anti-topoisomerase anti-RNA polymerase III | 3 |

**Table 1.** *these criteria are applicable to any patients considered for inclusion in a systemic sclerosis study. The criteria are not applicable to patient with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestation. # The total score is determined by adding the maximum weight in each category. Patients with a total score > 9 are classified as having definite systemic sclerosis. Source: ARD

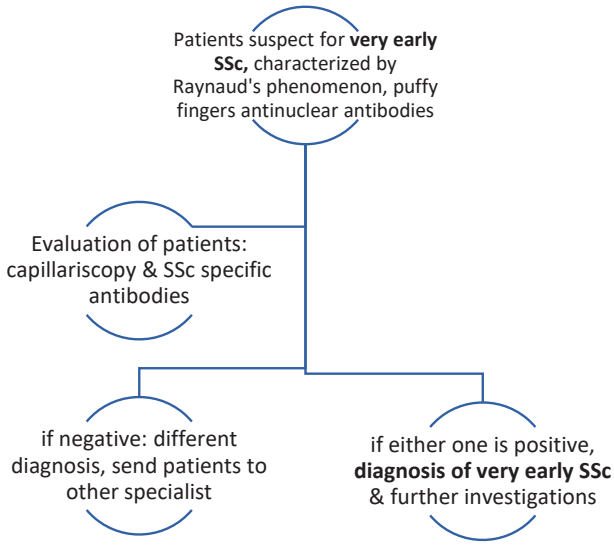


**Figure 1.** Very early SSc (VEDOSS) criteria.

*Pathophysiology*

SSc is characterized by a dysregulation in the innate and adaptive immune response, by vascular damage and excessive collagen deposition in the extracellular matrix [15]. The clinical and pathologic manifestations of SSc are the result of this triad: (1) innate and adaptive immune system abnormalities leading to production of autoantibodies and cell-mediated autoimmunity, (2) microvascular endothelial cell/small vessel fibroproliferative vasculopathy, and (3) fibroblast dysfunction generating excessive accumulation of collagen and other matrix components in all organs. From early autopsy studies we learned that multiple organ systems are involved in SSc pathogenesis as the following abnormalities were frequently found; interstitial lung fibrosis (74%), arteriolar thickening (29%), myocardial fibrosis (81%), pericardial lesions (53%), muscle atrophy and fibrosis of the esophagus (74%), lesions of reflux esophagitis (40%), muscle atrophy of the small intestine, dilatation and/or fibrosis of the duodenal loop or other segments of the small intestine (48%) and/or renal lesions (58%) [16]. Histologic examination of early SSc skin reveals changes consistent with damaged endothelial cells, including endothelial cells undergoing apoptosis, that precede the development of fibrosis by months to years. In addition, skin biopsies from SSc patients with a longer disease duration show a significant increase in myofibroblasts. In the end, as the vessels of the vascular system lose their elasticity, the vessel media and adventitia become fibrotic and more prone to vessel occlusion; which results in end organ damage. There is a certain interplay between these three characteristics (immunity, vascular system and fibrosis). However, it has not yet been established which of these processes is of primary importance, or how they are related during the development and progression of the disease [17]. There are reasons to presume that vasculopathy and dysregulated immunity precedes fibrosis in SSc. It remains unclear whether the activation of immune pathways ultimately drives the disease pathogenesis or rather represents a defective attempt to limit or even reverse excessive extracellular matrix deposition and progressive vasculopathy [18].

*SSc specific autoantibodies*

Current research is indicating a prominent role of both the innate and adaptive immune response in SSc pathophysiology. In addition, the SSc specific autoantibodies produced by B cells have important diagnostic and prognostic values in SSc [17, 19]. B cell receptors and T cell receptors are the proteins on which adaptive immunity is based. Effector B cells, called plasma cells, secrete soluble forms of B cell receptors, namely Immunoglobulins or antibodies, the main weapon of the adaptive immune response. These antibodies are used by the immune system to identify and neutralize foreign objects such as pathogenic bacteria and viruses. The antibody recognizes a unique part of the pathogen, the antigen. An autoantibody is mistakenly targeting and reacting with non-foreign proteins commonly expressed human tissue. In SSc, disease specific

autoantibodies recognize self-proteins that are commonly expressed in the nucleus of human cell, so-called anti-nuclear autoantibodies (ANA). ANA are detected in more than 95% of the SSc patients. Anti-centromere antibody (ACA), anti-topoisomerase antibody (ATA) and anti-RNA polymerase III autoantibodies (ARA) are the most specific and most prevalent in SSc. These SSc specific autoantibodies bear clinical significance as biomarkers to help with early diagnosis and prediction of the disease course, and they might also be helpful to understand pathophysiological processes of the disease [20]. Presence of ACA in SSc patients is associated with limited cutaneous SSc (lcSSc), calcinosis and GI involvement [20, 21]. Presence of ACA generally carries a better prognosis than many other SSc associated autoantibodies with respect to survival. ATA is associated with diffuse cutaneous SSc (dcSSc), ILD and their presence indicates an unfavorable prognosis [22, 23], ARA is associated with rapid progressive skin involvement and renal crisis. Evidence suggests an active role for SSc specific autoantibodies in the pathogenesis process beyond associations with the disease [18, 24-27]. In addition to their role as diagnostic biomarkers, each of the different autoantibodies correlates with typical clinical phenotype which suggests that the immune response involved in these specific autoantibody production may play a role in disease pathophysiology. However, the exact role of the SSc specific autoantibodies remains unclear [28, 29].

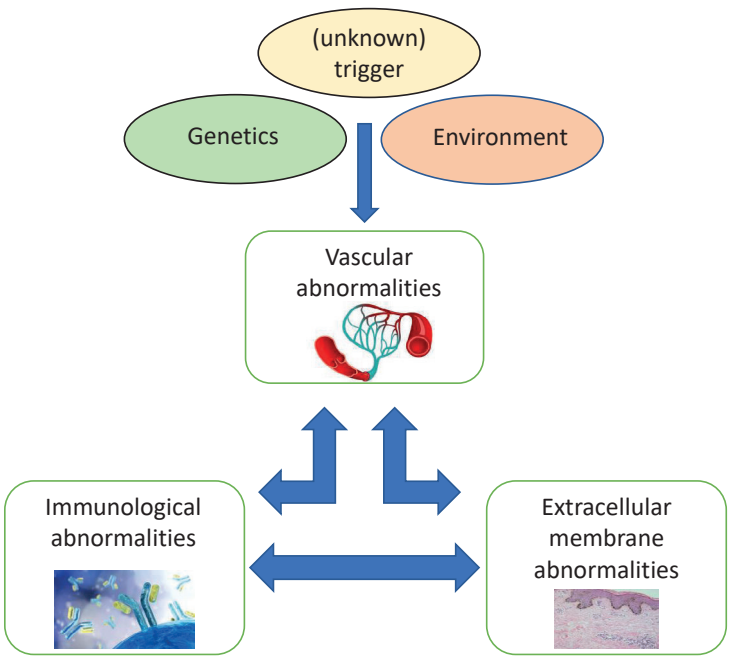


**Figure 2.** Schematic overview of SSc pathogenesis. Source: Annu. Rev. Pathol. Mech.Dis.2011.6:509-537

*Microangiopathy*

Clinically, obliterative microangiopathy leads to RP symptoms, and these symptoms precede other SSc symptoms by many years. RP with microvascular damage appears to be one of the best predictors of development of SSc [30]. Microvascular damage is characterized by alterations of the capillaries with a decrease in capillary density, enlarged capillaries, hemorrhages, disorganization of the vascular array and an abnormal morphology. Some suggest that vascular injury is the primary mechanism driving pathogenesis in patients with SSc [31-33]. A spectrum of changes can be seen in the vascular system that ranges from endothelial cell activation with enhancement of inflammatory properties, and apoptosis with capillary destruction and devascularization of the tissues leading to defective angiogenesis and vasculogenesis. There are several hypotheses on how vascular alterations may lead to fibrosis. It has been reported that vascular endothelial cells (EC's) undergo endothelial-to-mesenchymal transition (endoMT), in which EC's acquire extracellular matrix producing myofibroblasts features [34]. Myofibroblasts play an important role in the fibrosis pathogenesis, and myofibroblast may arise from different sources including perivascular pericytes.

The structural alterations in the capillaries of patients with SSc are well recognized and studied by nailfold capillaroscopy (NC), a non-invasive and safe technique that determines the degree of microangiopathy by using standardized magnification to visualize the capillaries in the nailfold [35]. In SSc, specific patterns of capillary changes and the degree of these changes have been defined [36]. These specific changes have been incorporated both in the ACR/EULAR 2013 classification criteria for SSc, as well as in the criteria for very early diagnosis of SSc. More severe microangiopathy is associated with more severe disease and with disease progression in SSc patients, underlining the importance of microangiopathy in SSc pathophysiology [35, 37-44]. Next to disease specific autoantibodies, NC therefore can be seen as an important biomarker to diagnose SSc and to predict complications in SSc.

*Fibrotic changes*

One of the hallmarks in the pathogenesis of SSc is fibrosis of the skin and internal organs. Excessive extracellular matrix (ECM) deposition results in altered architecture of organs and tissues which in the end leads to dysfunction. In healthy persons fibrosis is seen as a process aiming at repair; in SSc the triggers for uncontrolled fibrosis are still poorly understood. Profibrotic mediators released from infiltrating leukocytes, activated endothelial cells, and degranulated platelets may be the cause of fibroblast activation and collagen release during the early stages of fibrosis. Endogenous activation of fibroblasts due to epigenetic modifications or biochemical or physical factors may play a role in disease progression later in the disease course [45, 46].

*Survival and treatment*

The overall survival of SSc has improved over the last couple of years. This is assumed to be at least partly caused by earlier initiation of adequate treatment based on regular screening and greater awareness for organ involvement [47]. Survival rates at 1,5 and 10 years of disease are 94.2%, 80.0% and 65.7% respectively, with cardiopulmonary involvement as number one cause of death in SSc [6]. Treatment options in SSc consist of supportive medication on the one hand and therapies that aim to reduce inflammation, fibrosis and vasculopathy on the other hand [48]. Patients are treated based on their clinical manifestations and related severity. Treatment of fibrotic complications consists mainly of immunosuppressive drugs combined with symptomatic treatment. Vascular complications including PAH, digital ulcers are treated with vasoactive drugs including phosphodiesterase inhibitors and endothelin receptor antagonists; renal crisis is treated with ACE-inhibitors. Methotrexate is often the first choice for skin involvement, Mycophenolate Mofetil (MMF) or Cyclophosphamide should be considered for the treatment of SSc-related ILD, in particular in patients with progressive ILD [48]. In SSc patients with rapid progressive disease and high risk of early mortality, including skin and long involvement, hematopoietic stem cell transplantation is the best treatment option [49]. The last years evidence has been provided that anti-fibrotic treatment by direct inhibition of fibroblast activation (nintedanib) might be benefical in SSc. Treatment with nintedanib was shown to decrease the deterioration of pulmonary function in patients with SSc-ILD [50]. Unfortunately several clinical trials evaluating efficacy of different immunosuppressives failed to meet the primary endpoint [51-53]. Several explanations might account for this failure. Besides true inefficacy of a specific drug, also the lack of reliable outcome measures and clinical heterogeneity of the disease with lack of adequate biomarkers to identify the right target population might account for this. In conclusion, currently, in SSc patients it remains difficult to decide when, who and with what to treat. Multiple international trials are still gathering data on new possible treatments for SSc and new trials start on a yearly basis.

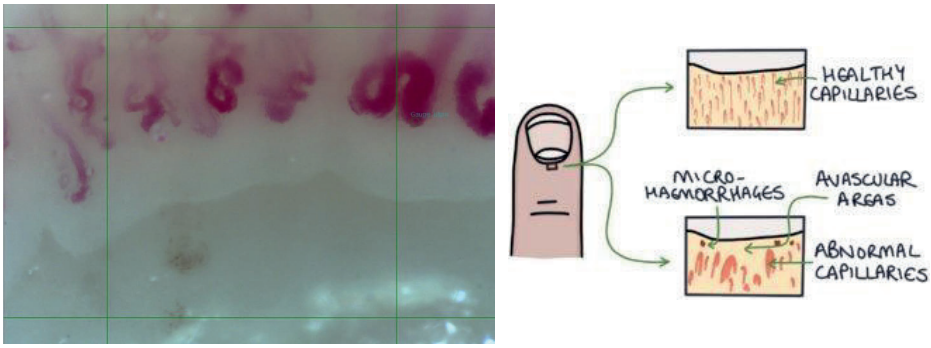


**Figure 3.** Image of nailfold capillaroscopy with a 1mm grid (Inspectis Pro videocap LUMC and https://zerotofinals.com/). We see an abnormal pattern (active SSc pattern, with capillary loss and dilatations).

# AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to identify biomarkers for risk stratification in SSc. Accurate biomarkers ensure that the correct patients are managed with the appropriate follow-up strategy and treatments at a time when this will have meaningful impact on the disease course.

**Part I Impact of Systemic Sclerosis on patients**
In the first part of this thesis we evaluate the impact of SSc and the impact of disease specific characteristics on SSc-related quality of life. We realized that there is little to no information if and how a diagnosis of SSc can impact patients' life in both mild and severe disease, and with the switch towards earlier diagnosis this is critical information. Therefore, in **chapter 1** we evaluated the illness and risk perceptions in recently diagnosed SSc patients in a small explorative study. In **chapter 2** we evaluated which disease specific characteristics have the largest impact on quality of life and on the evolution of quality of life over time in SSc patients.

**Part II Disease progression in Systemic Sclerosis**
Part II describes disease progression in SSc from different angles. First, in **chapter 3** we describe in detail the prevalence of disease progression in the Leiden cohort, for all organ domains. Second, we focus on gastro-intestinal involvement and it's progression over time by combining data of two large prospective cohorts in **chapter 4**, and finally in **chapter 5** we evaluate whether disease progression can be predicted at an individual level by applying machine learning.

**Part III Role of microangiopathy and specific autoantibodies in Systemic Sclerosis**
In the last part of this thesis, we investigated the role of two well-known biomarkers more extensively. In **chapter 6** we assess the associations between SSc specific autoantibodies and the degree of microangiopathy, and we also evaluated the association between sex and the degree of microangiopathy in the existing literature. In **chapter 7** we focus on a very specific rare autoantibody associated with SSc, anti-U3RNP autoantibody (anti-fibrillarin), we assess the prevalence of cardiopulmonary involvement in these patients, the degree of microangiopathy as shown by NC, and the association between NC and cardiopulmonary involvement. In **chapter 8** we evaluate whether ACA and ATA specific isotype expression and organ involvement associates with the degree of microangiopathy in SSc. As last, in **chapter 9** we investigate whether we can use the ACA isotype response as a biomarker to predict which ACA positive SSc patients progress over time.

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