Systemic sclerosis: can we identify patients at risk?

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Part II

Disease progression in Systemic Sclerosis

Chapter 3

Disease progression in Systemic Sclerosis

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DEAR EDITOR,

Systemic sclerosis (SSc) is a heterogeneous disease in which vasculopathy and fibrosis affect multiple organ systems such as the skin, gastrointestinal tract, kidneys, heart and the lungs (1). The clinical course of the disease can vary from rapidly progressive resulting in generalized fibrosis of the vital organs to a more indolent form developing over an extended period of time. For both physicians and patients, SSc represents a major clinical challenge, as prediction of the disease course remains difficult. Disease progression has been shown to occur often (2,3). However, many studies have been performed in selected subgroups of patients or have focused on specific organ domains.

In order to improve prediction of the individual disease course, we need accurate and complete information on the occurrence rate of disease progression per organ system during follow-up, preferably in an unselected cohort of SSc patients. This is crucial as in many SSc cohorts mild cases are not extensively followed, making these cohorts ungeneralizable to the entire SSc population. The Leiden Combined Care In SSc Cohort (4) has, from its beginning, included patients in accordance with the ACR/EULAR 2013 criteria (5). All included patients undergo extensive annual assessment irrespective of symptoms, and as such, data of this cohort can provide data on disease progression in an unselected SSc cohort. We analyzed occurrence of disease progression in 492 SSc patients fulfilling ACR/EULAR SSc 2013 criteria who underwent at least two complete assessments for organ involvement (4). Of the included patients, 79% (n= 389) was female; mean age at baseline was 55 years (SD 14); the median disease duration since first non-Raynaud symptom was 3.2 years (IQR 0.9-10.3), 39% (n= 194) were anti-centromere antibody (ACA) positive, 24% (n= 116) anti-topoisomerase antibody (ATA) positive, 6% (n= 27) anti-RNA polymerase III (anti-RNPIII) positive and 12% (n= 61) were anti-nuclear antibody (ANA) negative. Twenty-four percent (n= 118) of the patients had diffuse cutaneous SSc at baseline, and 37% (n= 183) had signs of interstitial lung disease (ILD) at baseline.

Disease progression was defined as progression in one or more organ systems, death, or start of immunosuppressive treatment, and was evaluated annually. For ILD, pulmonary arterial hypertension (PAH), modified Rodnan Skin Score (mRSS) and renal crisis, progression was defined as described previously (6,7) (supplementary file table S1 for detailed explanation). Cardiac progression, gastro-intestinal progression and myositis were each defined using a combination of variables (supplementary file table S1 for detailed definitions).

In 492 SSc patients (2109 timepoints, range follow-up 2-10 years [see supplementary file table S2 for differences in follow-up per subgroup]), disease progression was observed in 52% (n= 257) after a median follow-up duration of 4 years (range 1-8 years), including cardiac progression in 29% (n= 142), lung progression in 23% (n= 114), skin progression in 16% (n= 79), and GI progression in 12% (n= 60). Death (12%, n= 60), development of PAH (4%,n= 20), myositis (3%,n= 14) and renal crisis (1%,n= 5) occurred less frequently. Forty-eight percent of the patients (n= 235) did not show any progression during a median follow-up of 3 years (range 1-9) (82% female, 18% ATA+)

Current literature indicates SSc disease progression occurring most often early in disease course, specifically in ATA positive patients. Therefore, we evaluated disease progression during follow-up stratified for disease duration, autoantibody subgroup and disease subset (Figure 1 A,B,C and Figure S1 supplementary file).

In our cohort, 56% of observed progression occurred within 5 years since first non-Raynaud symptom. While progression in skin involvement occurred more frequently in early disease, proportion of patients with lung, heart or GI progression was relatively stable over time. In total 24% (n= 63/257) of first time organ progression occurred after 10 years since first non-Raynaud. When stratifying for both autoantibody and disease duration, we saw a striking difference in occurrence of skin progression: while in ATA patients this typically occurred early, the proportion of patients with skin progression increased over time in the ACA group. Cardiopulmonary progression was more frequent in ATA patients (58% of ATA showed cardiopulmonary progression), but also frequently observed in ACA patients (26% of ACA showed cardiopulmonary progression), and independent of disease duration in both groups. In ACA positive patients the percentage of progressors was often highest in the subgroup with longstanding disease. Unfortunately, we were underpowered to draw firm conclusions on progression rates in anti-RNPIII positive patients and ANA negative patients (supplementary figure S1). In addition to antibody specificity, also pattern of skin involvement has been identified as important clinical biomarker for risk of disease progression. Of the patients that presented with lcSSc, 17% progressed to dcSSc, most frequently within 5 years since first non-Raynaud. Any progression (excluding progression to dcSSc) occurred in 47% of lcSSc and in 72% of dcSSc (supplementary figure S1). Finally, one might hypothesize that follow-up duration might be different depending on clinical severity of the disease; however, in our cohort clinical follow-up was remarkably comparable for the clinical subgroups we evaluated (supplementary table S2), which supports that patient were evaluated annually independent of disease severity.

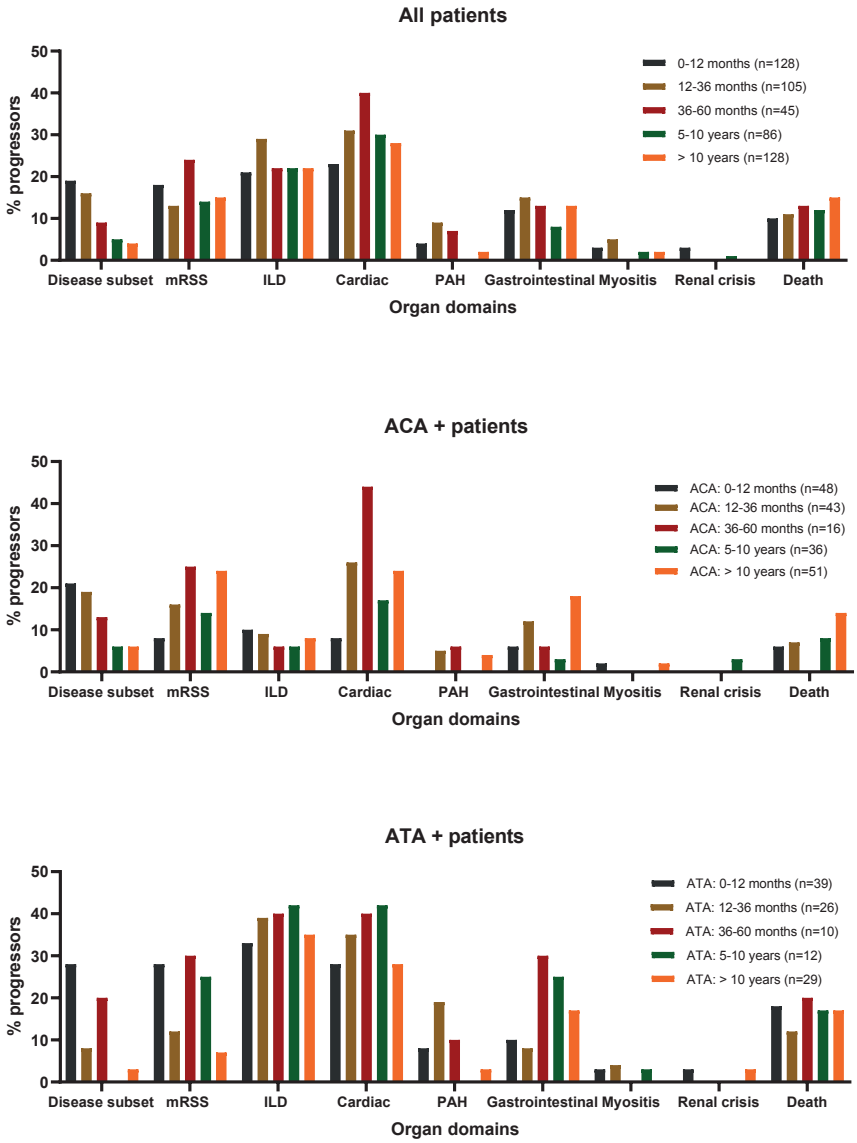

Figure 1. Percentage of progressors per subdomain. A. Stratified for disease duration since first non-Raynaud symptom, B. Stratified for anti-centromere (ACA) positive patients and disease duration, C. Stratified for anti-topoisomerase (ATA) positive patients and disease duration. mRSS= modified Rodnan Skin Score, ILD= interstitial lung disease, PAH= pulmonary arterial hypertension, n= number.

In conclusion, our data confirm that the proportion of SSc patients that experiences disease progression over time is substantial, also when applying ACR 2013 criteria that were designed to diagnose SSc earlier. We show that among ACA positive patients skin progression does occur, typically in longstanding disease. Finally, our data indicate that cardiopulmonary progression can occur at any time during follow-up, independent of disease duration, underlining the importance of identifying biomarkers for risk stratification that can guide follow-up. The challenge remains to identify individual patients with a low risk of progression and in whom annual complete assessment might be redundant. This justifies our ongoing research in identifying autoantibody levels and characteristics that could contribute to personalized risk stratification [work in progress] (7-8).

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SUPPLEMENTARY DATA

Supplementary table S1. Detailed explanation disease progression per organ system

Pulmonary progression	≥ 10% relative decline in forced vital capacity (FVC) with follow-up FVC < 80% predicted or ≥ 5% to < 10% relative decline in FVC and either a ≥ 15% relative decline in diffusing capacity of the lung for carbon monoxide (DLCO) with follow-up DLCO < 80% predicted or increase of the extent of lung involvement (interstitial lung disease (ILD)) as determined by HRCT
Cardiac progression	Based on a combined definition, which included clinical cardiac involvement, decreased left ventricular ejection fraction < 54% (LVEF), arrhythmias (> 2% ventricular extrasystoles, atrial fibrillation), and major cardiac events (including all acute coronary syndromes and pacemaker implantations).
Pulmonary arterial hypertension (PAH)	Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC), pulmonary capillary wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance > 3 Wood units, was classified as progression.
Gastro-intestinal	Development of gastric antral vascular ectasia (GAVE), or anemia AND weight loss (> 10% in 1 year).
Skin progression	mRSS increased ≥ 5 points and ≥ 25%
Renal progression	Clinical diagnosis of renal crisis (including hypertension, increase in creatinine, oligo/anuric renal failure)
Myositis progression	Diagnosis of myositis based on muscle complaints and histologic prove of myositis or complaints of myositis and an increased creatine kinase (>150 U/l) not otherwise explained AND muscle weakness.

Supplementary table S2: follow-up duration starting from first non-Raynaud for different clinical subsets in years

Subgroup	Follow-up duration starting from first non-Raynaud symptom, median (IQR)
ACA +	8.9 (4-14)
ATA+	8.4 (3-14)
ANA-	7.6 (4-16)
RNApIII +	9.5 (5-17)
LcSSc	9.2 (4-15)
DcSSc	9.0 (4-15)

ACA= anti-centromere antibody, ATA= anti-topoisomerase antibody, ANA= anti-nuclear antibody, LcSSc= limited cutaneous systemic sclerosis, dcSSc= diffuse cutaneous systemic sclerosis

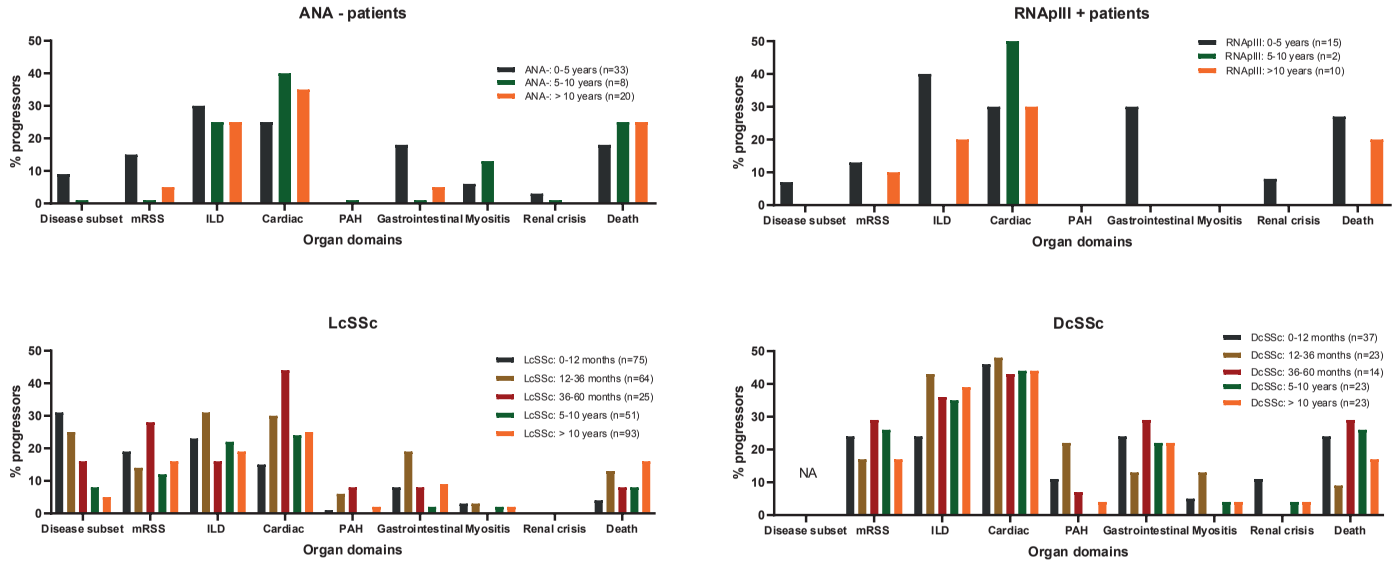

Figure S1. Organ progression stratified for disease duration since first non-raynaud symptoms, for disease subset and for autoantibody profile. ANA= anti-nuclear antibody, lcSSc= limited cutaneous systemic sclerosis, dcSSc= diffuse cutaneous systemic sclerosis, mRSS= modified Rodnan Skin Score, ILD= interstitial lung disease, PAH= pulmonary arterial hypertension.