The skin and its thickness

The registry and its data

The star and the sunflower

-

Bringing it all together

-

DeSSciphering Systemic Sclerosis

Inauguraldissertation

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Prof. Dr. Marcel Tanner, Prof. Dr. Ulrich A. Walker, Prof. Dr. Axel Finckh

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Prof. Dr. Martin Spiess

Dekan der Philosophisch-

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SUMMARY

Systemic sclerosis (SSc) is a rare, clinically heterogeneous, severe multisystem disorder characterised by autoimmunity, fibrosis and vasculopathy [Rodnan *et al.*, 1979; Gabrielli *et al.*, 2009]. It is one of the most disabling and disfiguring diseases among the systemic diseases and compared to other rheumatic diseases, SSc is associated with a high loss of life expectancy [Mok *et al.*, 2011].

Raynaud's phenomenon (RP) as an abnormality of the microcirculation is the initial and heralding symptom of SSc in over 95% of patients. Skin sclerosis and internal organ involvement then mostly manifest with a variable temporal interval after the onset of RP [Walker *et al.*, 2007; Varga *et al.*, 2012]. Aside from the skin, multiple organ systems can be damaged by fibrotic and/or vascular complications including the gastrointestinal tract, the pulmonary parenchyma and circulation, the heart, kidney and the joints [Medsger, 1997; Gabrielli *et al.*, 2009]. Although skin fibrosis is the cardinal feature of the disease, the progressive deterioration of internal organs determines the clinical outcome [Walker *et al.*, 2007; Domsic *et al.*, 2014; Nihtyanova *et al.*, 2014].

The aims of this thesis are (1) to map the time after disease onset in terms of RP to the onset of organ manifestations in SSc and to identify predictors of an early onset of manifestations; (2) to assess the effect of smoking on the manifestation and worsening of SSc organ manifestations and (3) to assess the level of functional ability and to identify factors associated with disability.

This thesis is based on the largest worldwide database for SSc, the European Scleroderma Trials and Research group (EUSTAR) registry. By today, more than 15,000 SSc patients are followed prospectively in more than 200 expert centres within the EUSTAR network.

We found that organ manifestations exhibit rapid kinetics early after the onset of RP, implying that there is only a short 'window of opportunity' to prevent incident organ damage. Furthermore, in every organ system, half of all organ manifestations become evident rather early in the disease, i.e. within the first two years. This implies that severe complications, for instance pulmonary hypertension and interstitial lung disease, are not restricted to late disease. Risk factors, such as the SSc subtype, autoantibody profile and the patient's sex do modify the cumulative incidences of the organ manifestations but do not substantially modify the steep

increase in organ complication rates during the first two years after RP onset. These results are of great importance for clinicians, who need to counsel, risk stratify and treat SSc patients early on after the diagnosis. Furthermore, the findings are of great significance for the design of therapeutics aimed to 'widen' the still very narrow 'window of opportunity'.

We demonstrated that the known adverse effect of smoking on the bronchial airways and alveoli is also observed in SSc patients. However, we did not observe robust adverse effects of smoking on the progression of SSc-specific pulmonary or cutaneous manifestations. This finding argues against a major role of tobacco-associated free radicals, vasoconstrictor and immunomodulatory effects in the pathogenesis of SSc vasculopathy and fibrosis.

Regarding the functional ability, we found that there is a major difference between the factors driving patient perceived levels of disability and those emphasized by physicians in their disease evaluation. The patients perceive dyspnoea, gastrointestinal symptoms, pain, muscle weakness and the presence of digital ulcers as the main factors driving their level of disability. These results that objective disease severity measures as assessed by the physicians do not correlate with patient-perceived disability indicate that the many and multi-faced aetiologies of disability and quality of life in SSc are poorly understood and are therefore a clarion call to further research.

LIST OF ABBREVIATIONS

ACA	Anticentromere Autoantibodies
ACR	American College of Rheumatology
ANA	Antinuclear Autoantibodies
Anti-RNAP-III	Anti-RNA Polymerase-III Autoantibodies
Anti-Scl-70	Anti-Topoisomerase Autoantibodies
CI	Confidence Interval
CSI	Comprehensive Smoking Index
DeSScipher	'To Decipher the Optimal Management of SSc'
DLCO/sb	Single Breath Diffusing Capacity for Monoxide (% of Predicted)
DU	Digital Ulcers
EULAR	European League against Rheumatism
EUSTAR	European Scleroderma Trials and Research Group
ESR	Erythrocyte Sedimentation Rate
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity (% of Predicted)
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
HR	Hazard Ratio
HRCT	High Resolution Computed Tomography
IIEF-5	International Index of Erectile Function
ILD	Interstitial Lung Disease
IQR	Interquartile Range
LVEF	Left Ventricular Ejection Fraction (%)
MCID	Minimal Clinical Important Difference
mRSS	Modified Rodnan Skin Score
NYHA	New York Heart Association
OR	Odds Ratio
PAH	Pulmonary Arterial Hypertension
PAPsys	Systolic Pulmonary Arterial Pressure as Estimated by Echocardiography (mmHg)
PF	Puffy Fingers

PH	Pulmonary Hypertension
PRO	Patient Reported Outcome
QoL	Quality of Life
RP	Raynaud's Phenomenon
SD	Standard Deviations
SHAQ	Scleroderma Health Assessment Questionnaire
SRC	Scleroderma Renal Crisis
SSc	Systemic Sclerosis
VAS	Visual Analogue Scale

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1. INTRODUCTION AND BACKGROUND

1.1 GENERAL INTRODUCTION

Systemic slcerosis (SSc; also called scleroderma) is a rare, chronic, connective tissue disorder affecting the skin as well as internal organs. SSc is characterised by three hallmarks: (1) a vascular microangiopathy, (2) a disorder of fibroblast function that enhances the synthesis of extracellular matrix and collagen, eventually leading to the characteristic skin thickening and fibrosis of visceral organs, and (3) some ill-defined immunological dysfunction, leading to the presence of diagnostically relevant SSc-related autoantibodies in the patients' circulation; in particular anticentromere (ACA), anti-topoisomerase (anti-Scl-70) and anti-RNA polymerase III (anti-RNAP-III) autoantibodies [Giordano *et al.*, 1986; Medsger, 1997; Steen, 1998; Wollheim, 2005; Gabrielli *et al.*, 2009; Hudson *et al.*, 2010]. A striking feature of SSc is the heterogeneity and the large variability in organ involvement, disease severity, the speed of disease progression, and survival between patients.

Among the different immune-mediated rheumatic diseases, SSc can be one of the most disabling and disfiguring diseases. Compared to other rheumatic diseases, SSc is additionally associated with the highest loss of life expectancy amounting to more than 30 years in female patients and 16 years in male patients [Mok *et al.*, 2011].

The aetiology and pathogenesis of SSc are complex, and the exact nature of the events underlying the development of the disease is still not fully understood [Abraham *et al.*, 2007, 2009]. Vascular and immunological processes are of central importance to the pathogenesis of SSc. However, the initial triggers and how initial events subsequently amplify and facilitate the development of the fibrosis and vasculopathy remains unclear [Piela-Smith *et al.*, 1994; Denton *et al.*, 1996].

SSc can be subdivided into limited cutaneous and diffuse cutaneous SSc. This diagnosis differs on the basis of the extent of skin fibrosis on the patients' bodies, or into SSc sine scleroderma if the patients have no detectable skin fibrosis [LeRoy *et al.*, 1988]. The SSc-specific autoantibodies are strong predictors of the patterns of organ involvements as well as disease outcome [Steen, 2005; Nihtyanova *et al.*, 2010].

Although skin fibrosis is the cardinal feature of the disease, the progressive deterioration of internal organs determines the clinical outcome [Walker *et al.*, 2007; Domsic *et al.*, 2014; Nihtyanova *et al.*, 2014]. The frequency and severity of manifestations partly depend on the subtype, and the autoantibody profile of the patients. However, patients suffer most frequently from Raynaud's phenomenon (RP), skin, gastrointestinal (GI) and musculoskeletal involvements and fatigue [Walker *et al.*, 2007; Lóránd *et al.*, 2014; Shreiner *et al.*, 2016]. Other frequent manifestations include digital ulcers (DUs), interstitial lung disease (ILD), pulmonary hypertension (PH), cardiac disease and renal crisis [Kahan *et al.*, 2009; Lambova *et al.*, 2010; Wells *et al.*, 2015; Hughes *et al.*, 2017].

In general, SSc is a progressive disease. The disease course and the speed of progression, however, varies with disease subtype and also with the presence and severity of manifestations early on in the disease [Nihtyanova *et al.*, 2014; Avouac *et al.*, 2016; Wu *et al.*, 2018]. Treating SSc patients is still a challenge, and there is no curative treatment. Hence, treatment recommendations focus on individual organ manifestations [Kowal-Bielecka *et al.*, 2017]. Autologous haematopoietic stem cell transplantation is at present the only disease-modifying strategy for the prevention of organ worsening, the improvement of skin and pulmonary function, consequently improving survival [van Laar *et al.*, 2014; Sullivan, Goldmuntz, *et al.*, 2018; Walker *et al.*, 2018].

1.2 EPIDEMIOLOGY

SSc is a rare disease, and population-based studies on SSc are relatively sparse. As it is the case in all connective tissue diseases, SSc is more prevalent in women than in men with estimated ratios mostly ranging between 3:1 and 6:1. However, the disease is more severe in male patients [Clements *et al.*, 2003; Chifflot *et al.*, 2008; Bernatsky *et al.*, 2009; Gabrielli *et al.*, 2009; Elhai *et al.*, 2016]. The onset of SSc peaks between the ages of 35 and 65 years; the average age of onset varies with sex and race [Mayes, 1997; Mayes *et al.*, 2003; Chifflot *et al.*, 2008].

Prevalence estimates also vary considerably from study to study mostly ranging between 50 to 300 per million [Medsger Jr. *et al.*, 1971; Silman *et al.*, 1988; Arnett *et al.*, 2001; Roberts-Thomson *et al.*, 2001; Mayes *et al.*, 2003; Allcock *et al.*, 2004; Le Guern *et al.*, 2004; Chifflot *et*

al., 2008; Nikpour *et al.*, 2010; Kuo *et al.*, 2011; Hoffmann-Vold *et al.*, 2012; Royle *et al.*, 2018]. The reported SSc prevalences in the US as well as in Australia are consistently higher than the estimates for Europe and Asia [Roberts-Thomson *et al.*, 2001; Mayes *et al.*, 2003; Allcock *et al.*, 2004; Chifflot *et al.*, 2008; Nikpour *et al.*, 2010; Kuo *et al.*, 2011; Barnes *et al.*, 2012; Hoffmann-Vold *et al.*, 2012; Royle *et al.*, 2018]. High prevalences of SSc are found in some native American groups, i.e., the highest ever reported prevalence was found in full-blood Choctaw Indian (4690 per million) [Arnett *et al.*, 1996].

Incidence estimates for SSc also vary considerably between studies, ranging from around 4 to 23 per million person-years depending on the population [Medsger Jr. *et al.*, 1971; Steen, Oddis, *et al.*, 1997; Mayes *et al.*, 2003; Chifflot *et al.*, 2008]. There is an ongoing discussion regarding whether the incidence has been increasing during the last decades despitethe lack of robust evidence for this [Chifflot *et al.*, 2008; Nikpour *et al.*, 2010; Royle *et al.*, 2018].

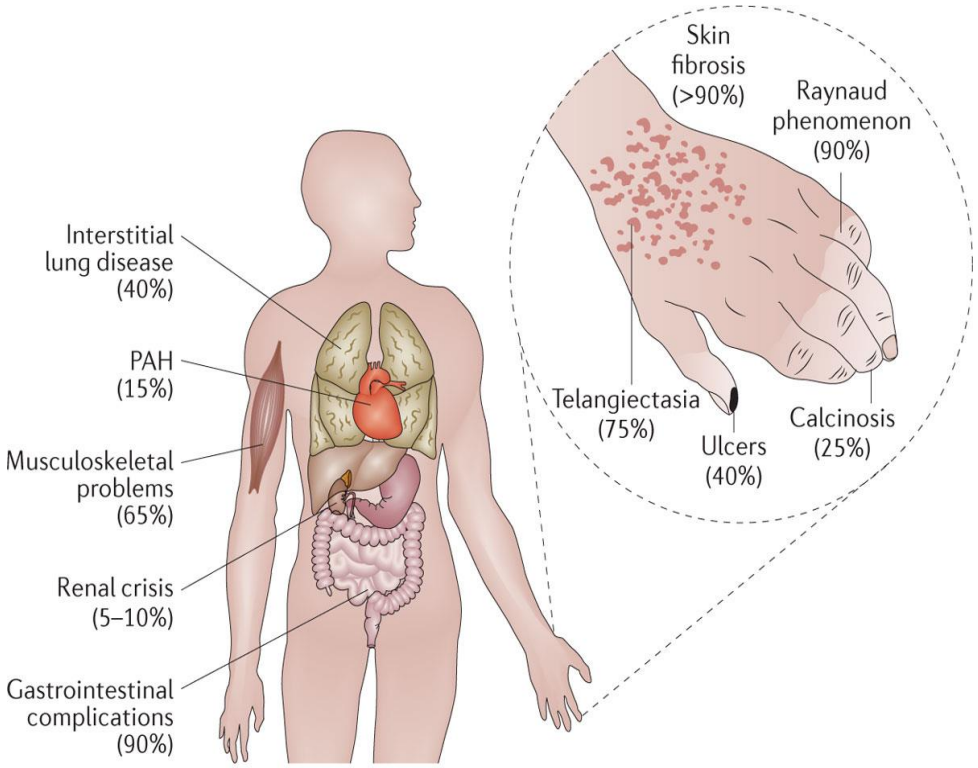
The considerable variation in the prevalence and incidence estimates might be partially reflecting the different classification criteria used in the studies. Additionally, this may also be due to differences in case ascertainment methodologies and therefore case completeness as well as greater disease awareness in some areas. These differences might also be true population differences caused by the populations' genetic background or environmental exposures, but also by the populations' demographic structure.

Several risk factors were reported to be associated with SSc development including genetic factors, race, age, sex, and environmental factors. Some of these factors are not only associated with SSc development but also with more severe disease. For example, African Americans have continuously been reported to have higher age and sex-specific incidence rates than whites, in some studies up to twice as high [Laing *et al.*, 1997; Mayes *et al.*, 2003]. However, African Americans do not only develop SSc more frequently, but they also suffer from more severe disease [Steen, Oddis, *et al.*, 1997; Greidinger *et al.*, 1998; Beall *et al.*, 2007; Steen *et al.*, 2012; Jaeger *et al.*, 2018].

1.3 MANIFESTATIONS

The systemic manifestations of SSc are diverse. Although skin fibrosis is the hallmark feature of SSc, multiple organ systems can be affected by fibrotic and/or vascular complications including the GI tract, the pulmonary parenchyma, the circulatory system, the heart, kidney and joints (**Figure 1**) [Medsger, 1997; Gabrielli et al., 2009; Allanore et al., 2015; Denton et al., 2017].

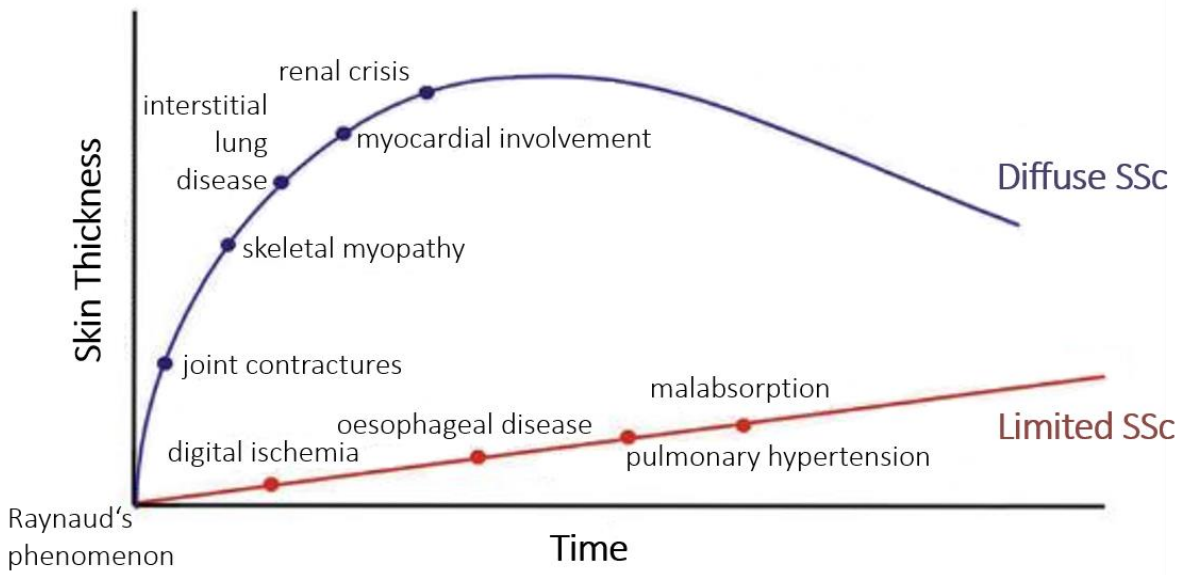
Figure 1. Organ complications associated with SSc (from [Allanore *et al.*, 2015])



The most common manifestations result from abnormalities in the microcirculation, with RP being most notable. RP is classically seen as a reversible vasospasm caused by functional changes in the small digital arteries of the feet and predominantly the hands and is triggered primarily by cold or stress [Wigley et al., 1996; Sunderkötter et al., 2006; Herrick, 2012]. RP is

the initial and heralding symptom of SSc in more than 90% of patients [Sunderkötter et al., 2006]. Skin sclerosis and internal organ involvement mostly manifest with a variable temporal interval after the onset of RP (**Figure 2**) [Walker et al., 2007; Allanore et al., 2015]. There is, however, a paucity of reliable, robust and evidence-based data on the temporal evolution of skin manifestations as well as on the temporal evolution of the internal organ manifestations as until now the knowledge on this timing (such as **Figure 2** [Varga *et a*l., 2012]) has only experienced-based. There is also a lack of knowledge of factors associated with faster development of these manifestations. As the various SSc manifestations constitute a crucial cause of morbidity and mortality, sound knowledge on when to expect the manifestations to occur is essential for physicians to risk stratify and counsel the patients early on after diagnosis. Additionally, such estimates of the patient's future trajectory of organ involvement are essential for the design of clinical trials aimed at altering the natural course of the disease. Therefore, one goal of this thesis was to longitudinally map the onset and identify risk factors for skin sclerosis and other SSc manifestations (**Aim 1; Article 1 and 2**).

Figure 2. Usual timing of organ involvement according to clinical experience (adapted from [Varga *et al.*, 2012])



As mentioned above, SSc is commonly divided into two main subtypes, namely limited cutaneous SSc and diffuse cutaneous SSc [LeRoy *et al.*, 1988]. In the limited cutaneous form, skin thickening is restricted to the hands, lower arms and the face. In the diffuse cutaneous form, the skin also thickens in body areas proximal to the elbows and knees [Gabrielli *et al.*, 2009]. Patients without skin fibrosis, i.e. 'SSc sine scleroderma', present with serological and clinical signs of SSc without detectable skin involvement [Hachulla *et al.*, 2011; Sullivan, Majhail, *et al.*, 2018]. Patients with limited or diffuse SSc have distinct patterns of organ pathology, speed of disease progression and outcomes (Figure 2 and Table 1). However, not all patients fit neatly into one of the subtypes [Varga *et al*., 2014].

Table 1. Clinical subsets in SSc (adapted from [Allanore *et al.*, 2015]).

Clinical subset	Clinical manifestations	Primary autoantibody antigens	Disease course
Limited cutaneous systemic sclerosis	• Distal skin fibrosis, sclerodactyly, telangiectasia, and calcinosis cutis may be prominent • Severe interstitial lung disease and scleroderma renal crisis are very rare	ACA	• Raynaud phenomenon may precede other manifestations • Slow progression with late development of pulmonary arterial hypertension (PAH)
Diffuse cutaneous systemic sclerosis	• Proximal skin fibrosis up to elbows and knees, including trunk • Tendon friction rubs may be present	Anti-Scl-70 and Anti-RNAP-III	• Rapidly progressive skin fibrosis • Early occurrence of renal, cardiac and pulmonary complications
Systemic sclerosis *sine* scleroderma	No detectable skin involvement	ACA	Raynaud phenomenon, nailfold capillary abnormalities, and PAH

Most SSc patients have highly specific circulating autoantibodies [Nihtyanova *et al.*, 2010]. The three most frequent types of antinuclear autoantibodies associated with SSc are ACA, anti-Scl-

70, and anti-RNAP-III autoantibodies. These autoantibodies are considered to be highly specific for SSc and are generally present exclusive of each other [Steen, 2005; Nihtyanova *et al.*, 2010; Heijnen *et al.*, 2013]. The type of autoantibody is strongly associated with distinct clinical manifestations, organ complications and risk of mortality (Table 1) [Ho et al., 2003; Ioannidis et al., 2005].

Anti-Scl-70 and Anti-RNAP-III autoantibodies are generally associated with diffuse cutaneous SSc [Gabrielli et al., 2009; Allanore et al., 2015]. Furthermore, anti-Scl-70 is associated with an increased risk of severe ILD, DU, and hand disability while anti-RNAP-III positivity is associated with rapidly progressing skin involvement, an increased risk of scleroderma renal crisis (SRC) and an increased risk of malignancies [Shah *et al.*, 2010, 2015; Nguyen *et al.*, 2011; Nikpour *et al.*, 2011; Moinzadeh *et al.*, 2014; Denton *et al.*, 2017]. In contrast, ACA is usually associated with limited cutaneous SSc and an increased risk to develop PAH [Steen, 2005].

The preventable and modifiable risk factor, smoking, has been established as an important environmental contributor to other autoimmune diseases such as rheumatoid arthritis [Saag *et al.*, 1997; Källberg *et al.*, 2011; Di Giuseppe *et al.*, 2014]. Unlike its role in rheumatoid arthritis, smoking does not confer a risk for development of SSc [Chaudhary *et al.*, 2011]. However, the association between smoking and SSc disease manifestations remains controversial as robust data with regards to a role of cigarette smoking exposure in the severity and the progression of SSc are scarce and limited to smaller, often cross-sectional studies. These results are of great importance firstly to clinicians who counsel and manage systemic sclerosis patients, and also to patients wondering about the effect of the modifiable risk factor smoking on their disease outcome. Therefore, one aim of this thesis was to rigorously assess this possible association between smoking and disease manifestations (Aim 2; Article 3).

Skin Involvement

Despite the heterogeneous clinical presentation of SSc, skin involvement is the cardinal feature of SSc and usually first develops distally in the fingers and hands [Krieg *et al.*, 2006]. Many patients initially experience non-pitting oedema of the fingers, erythema, and pruritus prior to the development of skin induration. Following this, the skin becomes firm, hard and tight, adhering to deeper structures and limiting movement. The thickening of the skin is caused by

an overproduction of collagen and extracellular matrix in the dermis and by temporary oedemata due to microvascular leaks [Clements *et al.*, 2004; Krieg *et al.*, 2006]. Commonly, skin thickness tends to increase over time especially in early diffuse SSc and then decreases in later stages [Denton *et al.*, 2017]. Skin sclerosis is present in almost all SSc patients; only less than 5% of patients have no skin sclerosis, i.e., SSc sine scleroderma [Krieg *et al.*, 2006; Denton *et al.*, 2017].

Whereas skin fibrosis *per se* is not causing increased mortality, severe or rapidly progressive skin involvement is associated with internal organ involvement leading to increased mortality [Shand *et al.*, 2007; Denton *et al.*, 2017]. Furthermore, skin involvement causes a substantial burden on patients' quality of life [Hudson *et al.*, 2009].

Skin thickening is most commonly quantified using the modified Rodnan skin score (mRSS) [Clements *et al.*, 1993; Pope *et al.*, 1995; Furst *et al.*, 1998]. The skin thickness at 17 anatomic sites is rated on a scale from 0 (normal) to 3 (most severe). The total skin score is the sum of the skin thicknesses at the 17 body sites with a possible range from 0 to 51 with higher values indicating a greater extent and severity of skin thickening [Krieg *et al.*, 2006]. The mRSS score has been validated as a reliable outcome measure and has demonstrated large effect sizes and sensitivity to change [Clements *et al.*, 1995; Kaldas *et al.*, 2009; Kumánovics *et al.*, 2017].

Digital Ulcers

DUs are a prevalent, external manifestation of vasculopathy [Steen *et al.*, 2009]. In around 50% of SSc patients, DUs occur at some time during the disease [Hachulla *et al.*, 2007; Steen *et al.*, 2009; Khimdas *et al.*, 2011] while around 10% to 15% of all SSc patients have 'current' DUs [Khimdas *et al.*, 2011; Ennis *et al.*, 2013]. DUs most commonly occur on the fingers, but also on the toes, causing local pain and often taking months to heal [Amanzi *et al.*, 2010; Hughes *et al.*, 2017]. DUs are associated with much of the morbidity associated with SSc and predict a worse disease course [Mihai *et al.*, 2016; Hughes *et al.*, 2017].

Gastrointestinal Involvement

The GI tract is the most frequently affected internal organ system with complications varying in severity and clinical effect. Approximately 90% of SSc patients suffer from GI manifestations with the upper and lower tracts being commonly affected largely owing to a disordered gastrointestinal mobility [Sandmeier *et al.*; Walker *et al.*, 2007; Schmeiser *et al.*, 2012; Shreiner *et al.*, 2016]. The most common symptoms include gastroesophageal reflux, bloating, distension, constipation or diarrhoea, and anorectal incontinence [Shreiner *et al.*, 2016; Denton *et al.*, 2017]. GI involvement may lead to severe malnutrition as well as weight loss which then carries a significant amount of morbidity in SSc [Omair *et al.*, 2012; Bharadwaj *et al.*, 2015; Codullo *et al.*, 2015].

Cardiac Involvement

Heart involvement in SSc is often clinically occult, and therefore its prevalence is probably largely underestimated. Any cardiac structure can be affected, and symptoms depend on the location of the cardiac pathologies [Kahan *et al.*, 2009; Boueiz *et al.*, 2010; Meune *et al.*, 2010; Parks *et al.*, 2014]. Clinical evident cardiac involvement has a poor prognosis as around a third of SSc-related deaths have a cardiac origin [Desai *et al.*, 2011; Elhai *et al.*, 2017]. Patients of both subsets, limited and diffuse, are at risk for cardiac pathologies; however, patients with diffuse SSc have higher incidences of cardiac complications [Steen *et al.*, 1988; de Groote *et al.*, 2008].

Pulmonary Involvement

Pulmonary manifestations are the leading cause of SSc-related deaths. The most common types of lung diseases in SSc are PH and ILD. The two manifestations have different pathogeneses, clinical features, and predictors.

Pulmonary Hypertension

PH is a frequent and severe SSc manifestation that occurs mainly in three forms: (1) isolated PAH, (2) PH secondary to ILD and (3) PH secondary to chronic left-heart disease [Launay *et al.*, 2017]. PAH is a disease of the small pulmonary arteries and is characterised by a progressive increase in pulmonary vascular resistance, right ventricular failure and ultimately death [Launay *et al.*, 2007]. The prevalence of PAH in SSc is around 5-15% [Mukerjee *et al.*, 2003; Walker *et al.*, 2007; Avouac *et al.*, 2010; Yang *et al.*, 2013]. Despite advances in the treatment arsenal, the prognosis of PAH patients is still poor with a median survival time of 3 years [Lefevre *et al.*, 2013]. PAH is typically seen in patients with longstanding disease and is more common in patients with limited SSc than in patients with diffuse disease [Shahane, 2013; Launay *et al.*, 2017].

Interstitial Lung Disease

SSc-related ILD is another severe, potentially fatal complication of SSc. In fact, interstitial lung involvement is the most frequent cause of death in SSc with around 35% of all SSc related deaths directly attributable to it [Steen *et al.*, 2007; Tyndall *et al.*, 2010]. Progressive fibrosis of the lung is an SSc hallmark and results from an excess synthesis and deposition of collagen [Schoenfeld *et al.*, 2015].

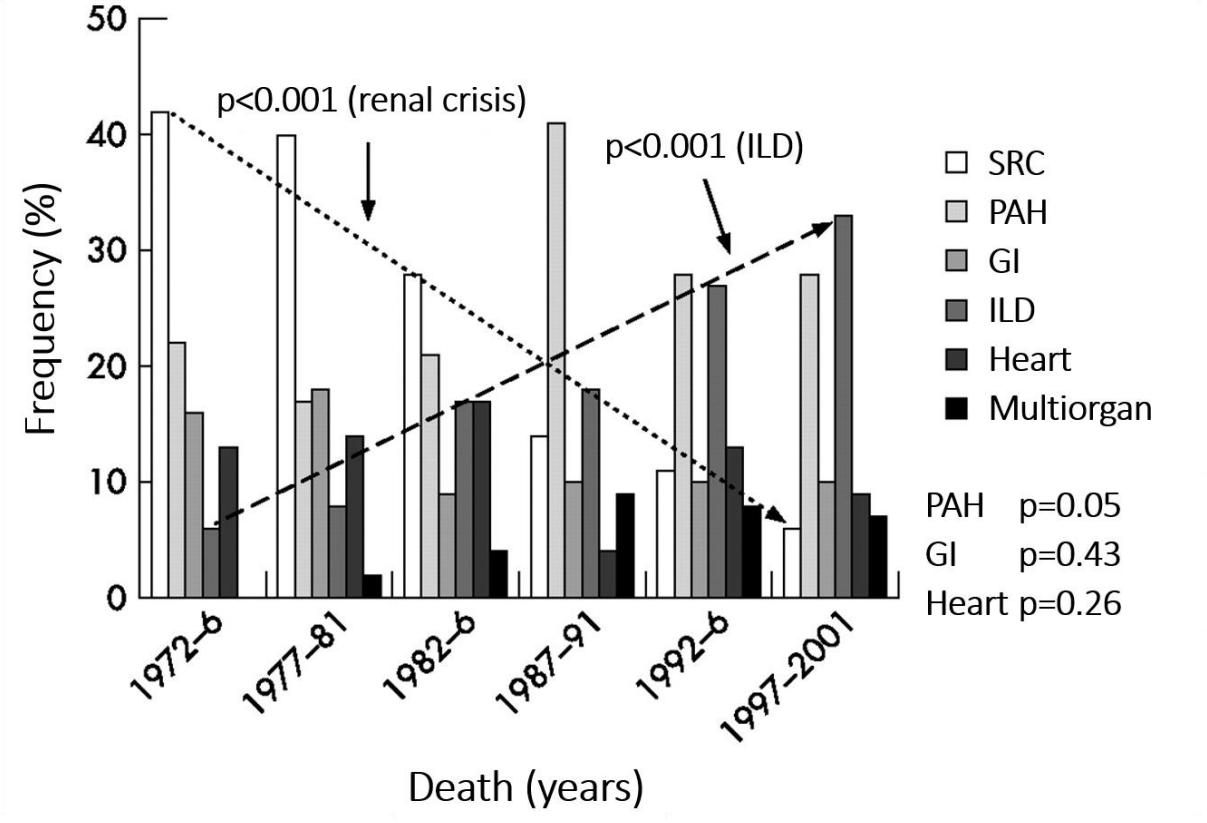
The spectrum of ILD severity ranges from non-progressive sub-clinical ILD to major pulmonary fibrosis and inflammation progressing ultimately to respiratory failure and death [Khanna *et al.*, 2010, 2011; Solomon *et al.*, 2013; Wells *et al.*, 2015]. ILD is present in around 80% of SSc patients but only around a third of patients develop progressive ILD [Khanna *et al.*, 2015; Denton *et al.*, 2017]. SSc-ILD is more prevalent in diffuse patients as it is in anti-Scl70 positive patients,and patients of African ancestry have a higher prevalence, incidence, and severity of SSc-ILD [Walker *et al.*, 2007; Steen *et al.*, 2012; Gelber *et al.*, 2013; Jaeger *et al.*, 2018]. Older age and a low FVC early on in the disease are associated with progression of ILD as well as death due to ILD [Winstone *et al.*, 2014; Schoenfeld *et al.*, 2015].

Renal crisis

Scleroderma renal crisis occurs in around 5-15% of SSc patients and is characterised by the sudden development of hypertension, thrombotic microangiopathy and renal failure [Steen, 1996; Muangchan *et al.*, 2013; Woodworth *et al.*, 2018]. Scleroderma renal crisis is most commonly present in patients with rapidly progressive diffuse SSc [Muangchan *et al.*, 2013; Allanore *et al.*, 2015]. Additionally, anti-RNAP-III positivity is strongly associated with renal crisis development as is corticosteroid therapy on medium to high dosage [DeMarco *et al.*, 2002; Nguyen *et al.*, 2010; Nikpour *et al.*, 2011; Iudici *et al.*, 2013].

While scleroderma renal crisis has been the most frequent cause of SSc-related mortality in the last century, it has become considerably less frequent during the last years possibly due to earlier diagnosis and/or aggressive use of preventive angiotensin-converting-enzyme inhibitors (Figure 3) [Steen *et al.*, 2007].

Figure 3. Changes in causes of SSc-related deaths between 1972 and 2001 (from [Steen *et al.*, 2007])



1.4 SURVIVAL

SSc has a profound impact on the life expectancy and continues to carry one of the highest risks of mortality of all connective tissue diseases [Elhai *et al.*, 2012; Rubio-Rivas *et al.*, 2014]. The reported mortality rates differ significantly between studies, though when pooled in meta-analyses the standardised mortality rates are around 2.7 to 3.5 compared to the general population [Elhai *et al.*, 2012; Rubio-Rivas *et al.*, 2014]. The average life expectancy of SSc patients is around 16 to 34 years less than in the general age, and sex-matched population [Mok *et al.*, 2011; Elhai *et al.*, 2012; Nikpour *et al.*, 2014].

The overall cumulative survival estimates are around 80% to 90% for a 5-year survival measured from the onset of RP and 60% to 80% for a 10-year survival [Lee *et al.*, 1992; Hesselstrand *et al.*, 1998; Arias-Nuñez *et al.*, 2008; Czirják *et al.*, 2008; Rubio-Rivas *et al.*, 2014]. However, the survival rates of patients vary greatly according to the extent of the skin involvement. The 10-year survival estimates in patients with diffuse SSc ranges from below 50% to around 70% whereas in patients with limited SSc the estimates are around 80% [Hesselstrand *et al.*, 1998; Arias-Nuñez *et al.*, 2008; Czirják *et al.*, 2008; Rubio-Rivas *et al.*, 2014]. Additionally, the distribution and severity of internal organ involvement, anti-Scl70 positivity, older age at onset and male sex are associated with increased mortality [Hesselstrand *et al.*, 1998; Arias-Nuñez *et al.*, 2008; Czirják *et al.*, 2008; Tyndall *et al.*, 2010; Hissaria, Lester, *et al.*, 2011; Rubio-Rivas *et al.*, 2014; Elhai *et al.*, 2017].

The causes of SSc-related deaths have changed over the past decades after the introduction of new therapies. The number of deaths related to SRC, once the predominant cause of death, has significantly reduced and nowadays pulmonary involvement, i.e., ILD and PH, is the leading cause of death (**Figure 3**) [Steen et al., 2007].

1.5 QUALITY OF LIFE AND FUNCTIONAL ABILITY

SSc, especially due to its chronicity and multi-organ manifestations, greatly affects the patients' physical and psychological functioning, and impairs their ability to participate in work and social activities [Johnson *et al.*, 2006; Hudson *et al.*, 2009; Sekhon *et al.*, 2010; Almeida *et al.*, 2015;

Frantz *et al.*, 2016]. Excluding stem cell transplantation, the treatment arsenal holds no definitive therapy or ability to change the disease profile. Therefore, one of the most important goals of care is to alleviate symptoms, disability, and to improve the health-related quality of life (QoL) and functional ability [Saketkoo, 2017; Walker *et al.*, 2018].

Various studies have identified SSc-related symptoms affecting the patients' QoL, functional ability and mental well-being, such as pain, GI symptoms, pruritus, fatigue, sleep problems, work disability and sexual dysfunction [Wagner *et al.*, 2000; Schieir *et al.*, 2010; Kwakkenbos *et al.*, 2015; Jaeger *et al.*, 2016; Nakayama *et al.*, 2016; Racine *et al.*, 2016]. However, due to the rarity of the disease, most of these studies have a limited sample size and focus on sub-populations, for example only patients with DUs or patients with PH [Chow *et al.*, 2008; Strickland *et al.*, 2012; Guillevin *et al.*, 2013; Lumetti *et al.*, 2015].

In clinical practice, the management of SSc patients is challenging. The physicians' main attention while caring for SSc patients is usually focused on objective measures of disease status and ultimately the survival of the patients. These measures may, however, not reflect the patients' experiences with the disease and the self-perceived impacts on QoL and functional capacity. Given the chronicity of the disease and the broad spectrum of manifestations with multiple organs involved, it is critical to consider the patients' perspectives. Therefore, one aim of this thesis was to analyse functional disability in a large and unselected cohort of SSc patients and to identify factors contributing to impairment as perceived by the patients (Aim 3; Article 4).

2. AIMS OF THE THESIS

This thesis aims to evaluate various organ manifestations in SSc and to identify possible risk factors for the severity of organ manifestations, the time to onset of these organ manifestations and their speed of worsening. In addition to evaluating these more clinical and objective measures of disease status, a further aim is to assess disease-related factors which the patients perceive as most burdensome and disabling in their life.

The specific research aims are:

Aim 1 To map the incidence and predictors of cutaneous, pulmonary, cardiac, gastrointestinal and renal involvement in the early course of SSc (**Article 1, Article 2**).

Aim 2 To assess the effects of smoking on the disease presentation as well as the on the speed of worsening of organ manifestations, namely lung involvement, skin involvement and DU in SSc (**Article 3**).

Aim 3 To assess the level of functional disability in a large cohort of SSc patients, and to identify patient perceived factors contributing to functional impairment (**Article 4**).

3. PATIENTS AND METHODS

3.1. PATIENT REGISTRIES

This thesis is entirely based within the European Scleroderma Trials and Research group (EUSTAR) registry and within the DeSScipher study, a ´top-on` project of the EUSTAR group.

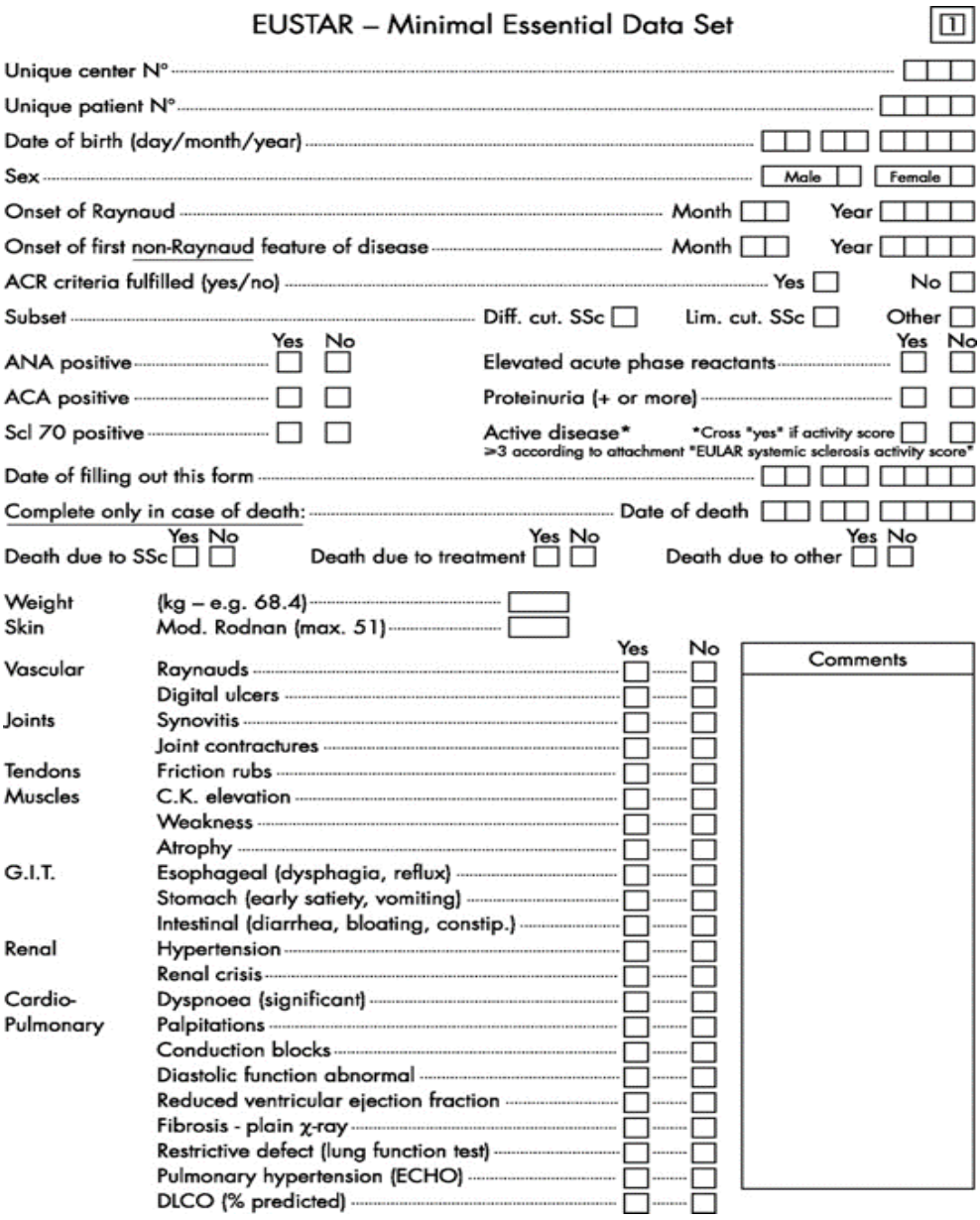
3.1.1. EUSTAR Registry

The EUSTAR group was founded in 2004 under the auspices of the European League against Rheumatism (EULAR) to foster the awareness, understanding, and research on SSc [Tyndall *et al.*, 2005; *EUSTAR*, 2018].

One of the integral parts of the EUSTAR group was the development of a 'minimal essential data set (MEDS)' to harmonise data collection across centres caring for SSc patients, therefore, allowing to longitudinally follow large patient groups which in terms allows sufficient sample sizes to answer an array of research questions (Figure 4). Due to the rare nature of the disease, this would not have been be possible without a large international collaboration.

The EUSTAR database was launched in 2004 with the 'minimal essential data set' and has been significantly extended over the last years [Tyndall *et al.*, 2005; Galluccio *et al.*, 2011; *EUSTAR*, 2018]. The EUSTAR network is mainly, however not exclusively, Europe-based and the database is by far the largest worldwide following SSc patients. Today, the network consists of more than 200 centres caring and prospectively and longitudinally documenting more than 15,000 SSc patients. Please see the EUSTAR website for an up-to-date list of all EUSTAR centres [*EUSTAR*, 2018].

Figure 4. Data collected with the original 'minimal essential data set' (from [Walker *et al.*, 2007])



EUSTAR – Minimal Essential Data Set [1]

Unique center N°
Unique patient N°
Date of birth (day/month/year)
Sex — Male — Female
Onset of Raynaud — Month — Year
Onset of first non-Raynaud feature of disease — Month — Year
ACR criteria fulfilled (yes/no) — Yes — No
Subset — Diff. cut. SSc — Lim. cut. SSc — Other

	Yes	No		Yes	No
ANA positive			Elevated acute phase reactants		
ACA positive			Proteinuria (+ or more)		
Scl 70 positive			Active disease* (*Cross "yes" if activity score ≥3 according to attachment "EULAR systemic sclerosis activity score")		

Date of filling out this form
Complete only in case of death: — Date of death

	Yes	No		Yes	No		Yes	No
Death due to SSc			Death due to treatment			Death due to other		

Weight — (kg – e.g. 68.4)
Skin — Mod. Rodnan (max. 51)

		Yes	No
Vascular	Raynauds		
	Digital ulcers		
Joints	Synovitis		
	Joint contractures		
Tendons	Friction rubs		
Muscles	C.K. elevation		
	Weakness		
	Atrophy		
G.I.T.	Esophageal (dysphagia, reflux)		
	Stomach (early satiety, vomiting)		
	Intestinal (diarrhea, bloating, constip.)		
Renal	Hypertension		
	Renal crisis		
Cardio-Pulmonary	Dyspnoea (significant)		
	Palpitations		
	Conduction blocks		
	Diastolic function abnormal		
	Reduced ventricular ejection fraction		
	Fibrosis - plain χ-ray		
	Restrictive defect (lung function test)		
	Pulmonary hypertension (ECHO)		
	DLCO (% predicted)		

Comments

3.1.2. DeSScipher Study

DeSScipher is the acronym for 'to decipher the optimal management of systemic sclerosis'. It was a large international EU-funded research project, mainly consisting of five non-interventional, observational trials. The DeSScipher project aimed to improve the treatment

strategies for SSc and therefore improve the quality of everyday life for SSc patients. Specifically, the DeSScipher project aimed to evaluate the prevention and treatment of DUs (observational trial 1), the improvement of hand dysfunction by arthritis (observational trial 2), the prevention and treatment of ILD (observational trial 3), the development and prevention of PH (observational trial 4) and the development and prevention of severe heart disease (observational trial 5) [The DeSScipher Project, 2013]. An additional DeSScipher aim was to identify predictors of functional disability in SSc (Aim 3; Article 4).

The DeSScipher study was designed as a 'top-on' study of the EUSTAR database, i.e., the database was extended in a modular way so that EUSTAR centres also taking part in the DeSScipher project had access to the DeSScipher module of the database additionally to the EUSTAR part, whereas the other EUSTAR centres did not. DeSScipher patients as such were not selected for any specific organ manifestations, as the DeSScipher patient cohort consisted solely of EUSTAR patients being followed at DeSScipher centres during the DeSScipher project regardless of organ manifestations and eligibility into any of the DeSScipher observational trials. Please see the DeSScipher study's website for the DeSScipher consortium centres and DeSScipher contributing centres [The DeSScipher Project, 2013].

3.2. INCLUSION CRITERIA INTO EUSTAR AND DESSCIPHER

Initially, all SSc patients fulfilling the 1980 SSc classification criteria were included in EUSTAR [Masi *et al.*, 1980]. In 2013, the new 2013 ACR/EULAR SSc classification criteria were implemented in the database and patients fulfilling either were enrolled [van den Hoogen *et al.*, 2013]. As DeSScipher was a 'top-on' of EUSTAR, the same inclusion criteria applied.

3.3. DATA COLLECTION, MANAGEMENT, AND MONITORING

Any SSc patients followed in one of the 'EUSTAR centres' were (and still are) invited to take part in EUSTAR. The same applies to ´DeSScipher centres`. All patient-specific information entered into the EUSTAR database was pseudonymised using Soundex. The Soundex is an algorithm in

which the family name and first name of the patient is used to create a string [Porta *et al.*, 2008]. The Soundex has the advantage that the care teams at the centres can search for their patients' data by their names, i.e., name to Soundex direction, but not the other way around, i.e., Soundex to name direction. The Soundex is also helpful in detecting duplicate patient entries.

Initially, data were collected on paper in each centre, faxed to the EUSTAR office and entered into an access database. In 2007, an online, browser-based database was established with an intuitive, easy-to-use web interface and the original data collected, i.e., the MEDS, were greatly extended [Tyndall *et al.*, 2005; Galluccio *et al.*, 2011; *EUSTAR*, 2018]. Since then, data are recorded locally within each centre.

Regular EUSTAR courses are offered to train physicians caring for SSc patients and therefore also improve EUSTAR's data quality [Czirják *et al.*, 2007]. In July 2013, an updated data model was implemented including extensive plausibility, validity and range checks to enhance data quality and reliability. Data quality within the DeSScipher project was additionally improved by off- and onsite data monitoring.

3.4. COLLECTED DATA, OUTCOME MEASURES AND COVARIATES

In the EUSTAR database, data are collected in a standardised form and are structured into patient's history, physical examination, tests and functions, lab results and medication. Data collected include:

- Patient's History

  Date of birth, sex, RP onset and current RP, date of the first non-RP SSc manifestation, GI symptoms, presence of dyspnoea and previous renal crisis;

- Physical Examination

  Fulfillment of the classification criteria for SSc, skin involvement, the presence of DUs and pitting scars as well as the presence of telangiectasia, tendon friction rubs, muscle atrophy and weakness and joint contractures and synovitis;

- Tests and Function

  Results of electrocardiography, echocardiography, right heart catheterisation, lung function test, x-ray and high-resolution computed tomography (HRCT) results;

- Lab Result

  SSc-related autoantibodies, creatinine kinase elevation, hypocomplementaemia, proteinuria.

In the course of the 2013 database update, also questions on smoking status (current, ex, never) and smoking intensity (pack years) as well as the time since smoking cessation and the duration of smoking were also implemented. As part of the DeSScipher project the Scleroderma Health Assessment Questionnaire (SHAQ), a patient-reported outcome (PRO) measure assessing functional ability, was implemented.

EUSTAR and DeSScipher are strictly observational, however yearly patient visits are encouraged.

3.5. STATISTICAL ANALYSES

For aim 1, i.e. the analysis of the speed of onset of organ manifestations and their predictors, we used two main methods: (1) Kaplan-Meier analyses to assess the cumulative probabilities of developing disease features as a function of time after RP onset and (2) Cox proportional hazards regression analyses to assess the combined effect of potential risk factors.

For both analyses, the date of the visit at which the organ manifestation was first observed was used as the end time, i.e., the incident time point. Manifestations that were already present at the first visit were also regarded as incident. If a manifestation was never observed, the date of the last follow-up visit was set as the censor time.

Kaplan-Meier estimates were stratified by sex, age, autoantibody status, and diffuse or limited skin involvement and strata were compared with log-rank tests. Cox proportional hazards regression analysis was used to assess the combined effect of the *a priori* defined potential risk

factors sex, age, autoantibody status and the extent of skin involvement on disease manifestations.

In aim 2, we assessed the associations of smoking behaviour with (1) the presence and severity of disease manifestations and (2) the progression in disease severity with multiple linear and logistic regression analyses adjusting for age, sex, time since RP and since first non-RP manifestation, antibody status and skin involvement. We analysed the outcome progression downscaled to a rate-of-change-per-12-months. We opted for this approach instead of assessing the outcome levels at follow-up while adjusting for the baseline levels to avoid introducing a bias and also to avoid the possibility of substantially inflating the regression coefficient estimates and the introduction of spurious associations [Glymour *et al.*, 2005].

Three smoking metrics were modelled separately:

Model 1 never smoking *vs.* previous smoking *vs.* current smoking,

Model 2 smoking intensity using pack-years:

never smokers – 0 pack-years,
light smokers – 0-10 pack-years,
medium smokers – 10-25 pack-years,
heavy smokers – >25 pack-years

Model 3 comprehensive smoking index (CSI).

The CSI is an index incorporating smoking duration, time since cessation and smoking intensity into a single variable [Dietrich *et al.*, 2004; Leffondré *et al.*, 2006]. The CSI depends on two parameters: the half-life, i.e., the rate at which the smoking's impact decays over time, and the lag-time, i.e., the delay between smoking and its impact. Both of those parameters are estimated separately for each outcome, and hence the CSI is different for each outcome. We identified the best combination of estimates of the two parameters for each outcome by minimising the Akaike Information Criterion [Akaike, 1974].

In aim 3, we assessed the predictors of functional disability as measured by the SHAQ by means of univariable and multivariable linear regression analyses. We also assessed the predictors of functional disability separately in patients with diffuse and patients with limited SSc. For this,

we reduced the model and only included factors that were strong and clinically significant predictors of functional disability in the overall patient group or that were defined *a priori*.

The minimal clinical important difference (MCID) of the Health Assessment Questionnaire (HAQ) is stated to be ≥0.22 [Wells *et al.*, 1993]. As the SHAQ is based on the HAQ and has the same range, we also applied this threshold to the SHAQ and we treated a difference of ≥10mm as the MCID for the visual analogue scale (VAS) components of the SHAQ [Wells *et al.*, 1993; Dworkin *et al.*, 2008; Strand *et al.*, 2011].

Like most registries, EUSTAR/DeSScipher also has missing data. To deal with the potential problems of missing data, i.e. biased results and loss of precision, we decided to apply multiple imputation with chained equations for objectives 2 and 3 after assessing the missingness mechanisms, i.e. only for data for which at least the missing at random assumption holds [Sterne *et al.*, 2009; White *et al.*, 2010; Carpenter *et al.*, 2013]. Missing covariate values, as well as missing outcome values, were imputed 50 times. Missing data of categorical variables were either imputed with logistic regression, ordered logistic regression or multinomial logistic regression depending on the nature of the variable. We did not transform non-normally distributed numerical variables to preserve the possible associations of these variables with the other variables in the model. Instead, we used predictive mean matching based on the 20 nearest neighbours for all non-categorical variables [Little, 1988; Morris *et al.*, 2014]. The multiple imputation was carried out using the user-written *ice* command (Aim 3) and Stata's inbuilt *mi* command (Aim 2) [Royston, 2005, 2009; Stata Press, 2017].

All analyses were performed with Stata/IC version 13.1 and 15.1 (StataCorp, College Station, Texas, USA). For all aims, standard descriptive analyses were applied.

More details about the statistical analyses used can be found in the respective articles.

4. ORGAN INVOLVEMENT IN SYSTEMIC SCLEROSIS – WHEN DOES IT START?

ARTICLE 1: INCIDENCE AND PREDICTORS OF CUTANEOUS MANIFESTATIONS DURING THE EARLY COURSE OF SYSTEMIC SCLEROSIS: A 10-YEAR LONGITUDINAL STUDY FROM THE EUSTAR DATABASE.

Elina G. Wirz[1,2*], Veronika K. Jaeger[1*], Yannick Allanore[3], Gabriela Riemekasten[4,5], Eric Hachulla[6], Oliver Distler[7], Paolo Airo[8], Patricia E. Carreira[9], Mohammed Tikly[10], Serena Vettori[11], Alexandra Balbir Gurman[12], Nemanja Damjanov[13], Ulf Müller-Ladner[14], Jörg Distler[15], Mangtao Li[16], Peter Häusermann[2†], Ulrich A. Walker[1†], EUSTAR co-authors

[1] Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[2] Department of Dermatology, University Hospital Basel, Basel, Switzerland
[3] Department of Rheumatology A, Paris Descartes University, Cochin Hospital, Paris, France
[4] Department of Rheumatology, Charité University Hospital, Berlin, Germany
[5] German Rheumatism Research Centre (DRFZ), Leibniz Institute, Berlin, Germany
[6] Department of Internal Medicine, Hôpital Claude Huriez, University Lille, Lille Cedex, France
[7] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[8] Rheumatology and Clinical Immunology Service, Spedali Civili di Brescia, Brescia, Italy
[9] Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain
[10] Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[11] Rheumatology Department, Second University of Naples, Naples, Italy
[12] B. Shine Rheumatology Unit, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel
[13] Institute of Rheumatology, University of Belgrade Medical School, Belgrade, Serbia
[14] Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany
[15] Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany
[16] Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

**, †* *both authors contributed equally*

EUSTAR CO-AUTHORS:

Lidia Ananieva; Stefan Heitmann; Simona Rednic; Sergio Jimenez; Valeria Riccieri; Magdalena Szmyrka-Kaczmarek; Dominique Farge; Giovanni Lapadula; Marco Matucci-Cerinic; Serena Guiducci; Nicolas Hunzelmann; Maria Rosa Pozzi; Carina Mihai; Douglas Veale; Roger Hesselstrand; Eduardo Mariok; Vanessa Smith; Eugene J Kucharz; László Czirják; Duska Martinovic; Kamal Solanki; Codrina Mihaela Ancuta; Jean Sibilia; Caramaschi Paola; Manal Hassanien; Sarah Kahl; Adrianne Woods; Marie Vanthuyne; Ionescu Ruxandra; Sebastião C. Radominski; Andrea Lo Monaco; Ada Corrado; Michaela Koehm; Montecucco Maurizio; Bevcar Radim; Esthela Loyo; Maria Üprus; Raffaele Pellerito; Thierry Zenone; Armando Gabrielli; Otylia Kowal-Bielecka; Blaz Rozman; Raffaella Scorza; Lesley Ann Saketkoo; Oyvind Midtvedt; Carlos Alberto von Mühlen; Jörg Henes; Ani Branimir; Paul Hasler; Sule Yavuz; Peter Villiger; Brigitte Krummel-Lorenz; Magdalena Posa; Merete Engelhart; Christopher Denton; Dorota Krasowska; Paloma Garcia de la Peña Lefebvre; Franco Cozzi; Luc Mouthon; Sergio Jimenez; Edoardo Rosato; Selmi Carlo; Juan José Alegre Sancho; Carmel Mallia; Massimiliano Limonta; Matthias Seidel; Rosario Foti; Lisa Stamp; Susanne Ullman; Simon Stebbings; Vera Ortiz Santamaria; Francesco Del Galdo; Ellen De Langhe; Alessandro Mathieu; Cord Sunderkötter; Kilian Eyerich; Bojana Stamenkovic; Srdan Novak; Percival D. Sampaio-Barros; Cristiane Kayser; Ira Litinsky; Maura Couto

CORRESPONDING AUTHOR: Ulrich A Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland; Phone: +41 61 32 87479; Fax: +41 61 26 59021; E-mail: ulrich.walker@usb.ch

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CONTRIBUTORSHIP: Study design: UAW, VKJ; Analysis of data: EW, VKJ, UAW; Interpretation of data: EW, VKJ, UAW, OD, PH; Acquisition of data: UAW, YA, GR, EH, OD, PA, PEC, MT, SV, ABG, ND, UML, JD, ML; All authors were involved in drafting the article or revising it critically for important intellectual content and all authors approved the final version of the manuscript.

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ABSTRACT

Objectives

To longitudinally map the onset and identify risk factors for skin sclerosis and DU in patients with SSc from an early time point after the onset of RP in the EUSTAR cohort.

Methods

695 SSc patients with a baseline visit within one year after RP onset were followed in the prospective multinational EUSTAR database. During the 10-year observation period, cumulative probabilities of cutaneous lesions were assessed with the Kaplan-Meier method. Cox proportional hazards regression analysis was used to evaluate risk factors.

Results

The median mRSS peaked 1.0 year after RP onset and was 15 points. The 1-year probability to develop a mRSS≥2 in at least one area of the arms and legs was 69%, and 25%, respectively. Twenty-five percent of patients developed diffuse cutaneous involvement in the first year after RP onset. This probability increased to 36% during the subsequent two years. Only 6%of patients developed diffuse cutaneous SSc thereafter. The probability to develop DU increased to a maximum of 70% at the end of the 10 year observation. The main factors associated with diffuse cutaneous SSc were the presence of anti- RNAP-III autoantibodies, followed by anti-Scl-70 autoantibodies and male sex. The main factors associated with incident DU was the presence of anti-Scl-70 autoantibodies.

Conclusions

Early after RP onset, cutaneous manifestations exhibit rapid kinetics in SSc. This should be accounted for in clinical trials aiming to prevent skin worsening.

INTRODUCTION

SSc is a multisystem autoimmune disorder, characterised by vasculopathy and excessive tissue fibrosis [Rodnan *et al.*, 1979; Gabrielli *et al.*, 2009]. Skin sclerosis is a hallmark feature of the disease and is most commonly measured with the mRSS by assessing skin thickness in 17 different body parts [Rodnan *et al.*, 1979; Clements *et al.*, 1995; Kaldas *et al.*, 2009]. Dependent on the distribution of skin sclerosis, patients are categorised, at the maximum of extent, as having either limited or diffuse skin involvement [LeRoy *et al.*, 1988]. Discrimination between limited and diffuse cutaneous SSc is important, as diffuse cutaneous SSc is associated with higher morbidity and mortality independent of autoantibody status [Walker *et al.*, 2007]. DU are cutaneous lesions caused by obliterative vasculopathy. Both, skin sclerosis and DU have proven to highly impact daily living and quality of life [Mouthon *et al.*, 2010; Bérezné *et al.*, 2011].

Several cross-sectional studies suggest that the prevalence of both, skin sclerosis and DU, depends on sex, age and autoantibody status [Walker *et al.*, 2007; Sunderkötter *et al.*, 2009; Hügle *et al.*, 2011; Khimdas *et al.*, 2011; Manno *et al.*, 2011; Hasegawa *et al.*, 2013; Alba *et al.*, 2014]. However, only few studies have prospectively investigated the impact of risk factors for cutaneous SSc lesions [Perera *et al.*, 2007; Hasegawa *et al.*, 2013]. Some of these studies were small, others did not investigate DU incidence, not able to capture the onset of skin sclerosis early during the disease course, or able to calculate incidences.

Given the paucity of pivotal data on the temporal evolution of skin manifestations during the early course of SSc, our goal was to analyse the incidence of skin sclerosis and DU in patients who developed SSc within one year after the onset of RP.

By using real-life data from the large multi-centre EUSTAR cohort [Walker *et al.*, 2007], we also assessed the skin sclerosis in different body areas, and determined factors associated with an unfavourable outcome in terms of acquisition of diffuse skin involvement and DU.

METHODS

Study population and design

The architecture of the multinational, prospective EUSTAR Scleroderma Trials and Research database has been described elsewhere [Walker *et al.*, 2007; Meier *et al.*, 2012]. In order to be able to document clinical data of patients, each participating centre obtained ethical approval by its local ethics committee; written informed consent was acquired from each patient registered. The demographic and disease characteristics of patients collected between the database inauguration in June 2004 and the date of censoring (18th February 2014) were exported, provided that the patients were older than 18 years at their first EUSTAR visit and fulfilled the 1980 ACR criteria for SSc [Masi *et al.*, 1980]. In order to capture patients early in their disease course, i.e. to simulate an inception cohort, the analysis was restricted to patients who had their first EUSTAR visit within one year after RP onset.

Several outcome measures were analysed as a function of time after RP onset: the evolution of the mRSS, the presence of skin sclerosis (defined as a mRSS≥2 points at the body area of interest), the presence of diffuse cutaneous involvement (defined as a mRSS≥2 points in at least one of the 6 skin areas proximal to the elbows and knees, i.e. upper arms, chest, abdomen, thighs) and the presence of DU (defined as ulcers distal to, or at the proximal interphalangeal joints, and not thought to be due to trauma). The effect of sex, age (dichotomised at the median age at RP onset) and autoantibody status on skin sclerosis and DU incidence were assessed in more detail.

Statistical analysis

Frequencies and percentages of categorical variables were compared using Pearson's X^2-tests. Means and SD, and for non-normally distributed variables additionally medians and IQR were reported; two-group comparisons were performed using Student's t-tests or Wilcoxon-Mann-Whitney-tests.

Using Kaplan-Meier methods we assessed the time to the first diagnosis of the manifestations. The date of the visit at which these were first observed was used as the end time. In case the

manifestation was already present at the first visit, the date of this first visit was regarded the end time. If the manifestation was never observed, the date of the last follow-up visit was regarded the censor time. Kaplan-Meier-estimates were compared by log-rank tests and incidence rates and their 95% CI were calculated. Cox proportional hazards regression analysis was used to assess the combined effect of the potential risk factors sex, age and autoantibody status on disease manifestations. All data were analysed using Stata 13.1 (Stata Corporation, Texas, USA).

RESULTS

Patient characteristics

At the time of the data export, the EUSTAR database included 9891 patients fulfilling the inclusion criteria. Of these, 695 patients had their first EUSTAR visit within one year of RP onset. These patients had a median observation time of 2.1 years (IQR 0.7-4.6; mean 3.1 years, SD 3.0). The patients included in our analysis were approximately 9 years older, had a higher baseline mRSS, and more frequently anti-Scl-70 or anti-RNAP-III autoantibodies than the patients excluded (Table 2). Furthermore, the percentage of men was significantly higher in the group analysed, than in the excluded group. In contrast, DU and ACA were less frequent.

Skin sclerosis by body area

We first aimed to describe the onset of skin sclerosis at different body areas (Figure 5). Most patients developed skin sclerosis within the first year after RP onset. The probability of having a mRSS≥2 in at least one area of the upper extremities within the first year was significantly higher than for the lower extremities (68.7%, 95%CI 63.8-73.6 *vs.* 25.0%, 95%CI 20.6-30.2).

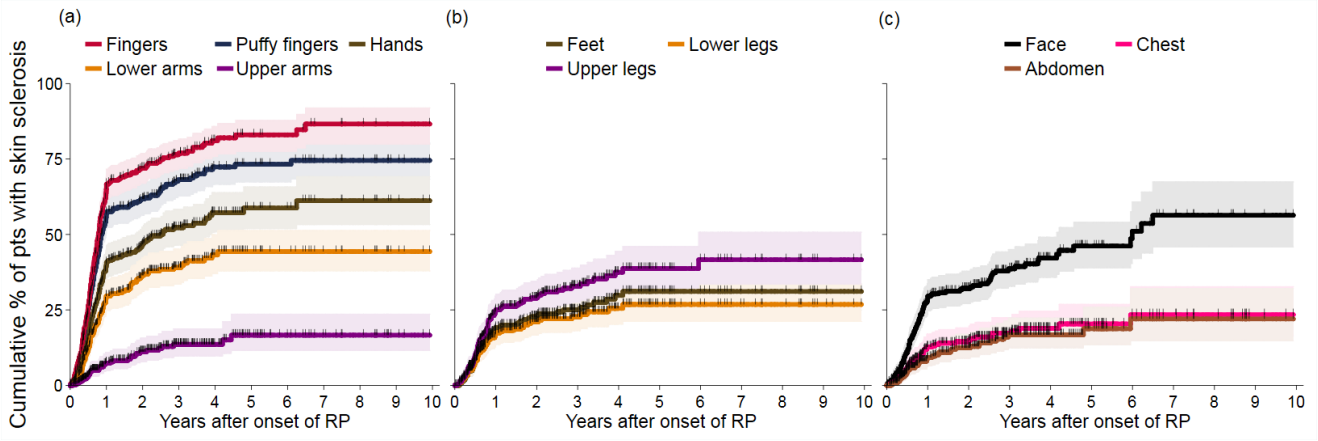
Table 2. Comparison of disease characteristics at the baseline visit between patients included in this analysis (visit within 1 year after onset of RP) and those excluded (no visit within 1 year after onset of RP).
*data on anti-RNAP-III autoantibodies only available for 317 (45.6%) of the included and 4187 (45.3%) of the excluded patients.

Patient characteristics at baseline visit	Included	Excluded	P-Value
Number of patients	695	9196	
Age at onset of RP, years; mean (SD)	51.7 (14.2)	42.4 (14.8)	<0.001
Male, %	26.6	13.3	<0.001
Laboratory parameters per patient			
ANA, %	96.1	96.4	0.67
ACA, %	16.7	34.7	<0.001
Anti-Scl-70, %	42.0	33.2	<0.001
Anti-RNAP-III*, %	9.5	2.9	<0.001
Disease characteristics per patient			
Age at onset of first non-RP, years; mean (SD)	50.9 (14.4)	46.3 (14.1)	<0.001
Digital ulcers, %	28.4	34.2	0.002
Puffy fingers, %	52.7	37.3	<0.001
mRSS; median (IQR)	10.0 (4.0-19.0)	6 (3.0-12.0)	<0.001
mRSS; mean (SD)	12.7 (10.5)	8.7 (7.7)	<0.001
Diffuse cutaneous involvement, %	20.6	9.0	<0.001

As expected, the highest incidence rate of skin sclerosis in the first year was observed at the fingers (105.7/100 patient years, 95%CI 92.9-120.1). At the more proximal areas of the upper extremities, the incidence in the first year was lower (**Figure 5a**). The incidence rate of puffy fingers in the first year tended to be lower than that of finger skin sclerosis (90.4/100 patient years, 95%CI 78.7-103.9), although this difference was not statistically significant. Similarly, the more distal areas of the lower extremities were more often affected than the more proximal areas (**Figure 5b**).

In the central body areas (**Figure 5c**), the rate of skin sclerosis at the face was similar to that of the forearms (42.1/100 patient years, 95%CI 34.4-51.5). The chest and abdomen had rates similar to the thighs (17.7/100 patient years, 95%CI 13.0-24.1 and 12.8/100 patient years, 95%CI 8.9-18.4, respectively).

Figure 5. Kaplan-Meier curves with 95%CI of patients developing skin sclerosis defined as ≥2 points at the area of mRSS scoring, separated for the upper extremities (a), the lower extremities (b), and the central body areas (c).
Hash marks illustrate censored observations.



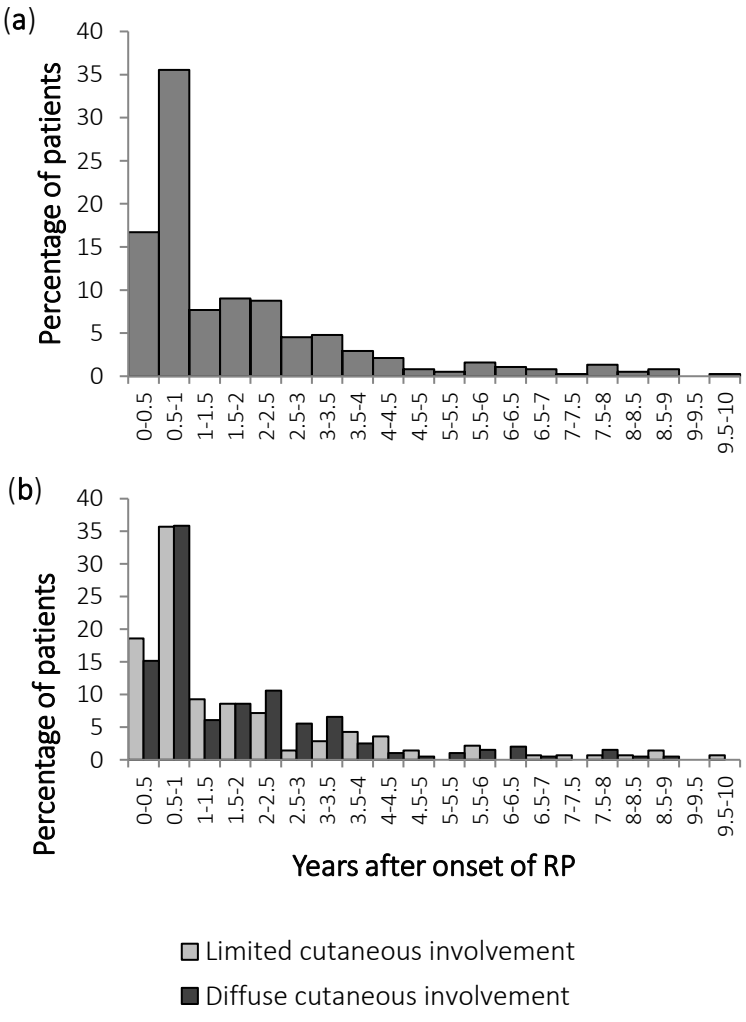
All patients who developed moderate to severe skin sclerosis (defined as a mRSS≥2 at any body area) did so within 6.5 years after RP onset. The probability to develop skin sclerosis within this period was 87.7% (95%CI 80.5-92.1) in the upper extremities, and 41.6% (95%CI 33.6-50.8) in the lower extremities, 23.4% (95%CI 16.5-32.7) at the chest and 22.0% (95%CI 14.8-32.1) at the abdomen.

When applying a less stringent definition of skin sclerosis, namely a cut off of ≥1 mRSS point at any body area, the probability of developing skin sclerosis was 94.7% (95%CI 88.5-98.2); as in the case of the more stringent definition for skin sclerosis, all patients developed this within 6.5 years after RP onset. Thus, about 5.0% of patients had SSc sine scleroderma.

We also analysed the time of mRSS peaking in patients with skin involvement who had multiple visits with a documented mRSS (n=381). The median peak mRSS was 15 points (IQR 7-24; mean mRSS 16.7, SD 10.5) and was reached as early as 1.0 year after RP onset (IQR 0.6-2.4; mean 1.9 years, SD 2.2; **Figure 6a; Supplementary Figure 1a**). Patients with limited cutaneous involvement reached the mRSS peak of 9.5 points (IQR 6-14; mean mRSS 10.4, SD 6.1) after a median of 0.9 years (IQR 0.6-2.2; mean 2.0, SD 2.5; **Figure 6b; Supplementary Figure 1b**). For patients with diffuse cutaneous involvement, the peak mRSS was 23 points (IQR 16-29.5; mean mRSS 22.8, SD 9.6) and was reached after a median of 1.0 year (IQR 0.6-2.5; mean 1.9 years, SD 2.0; **Figure**

6b; Supplementary Figure 1b). Thus, there was no difference in the median time to reach the mRSS peak between patients with diffuse and patients with limited cutaneous SSc (p=0.36). We also assessed other potential risk factors for the time to mRSS peaking in a multivariable analysis only including the first year after RP onset as half of the patients reached their maximal mRSS as fast as within this first year. In this analysis, neither patients' age and sex nor the presence of autoantibodies in the patients' sera was associated with the time to development of the maximal mRSS within the first year after RP onset (Supplementary Table 1).

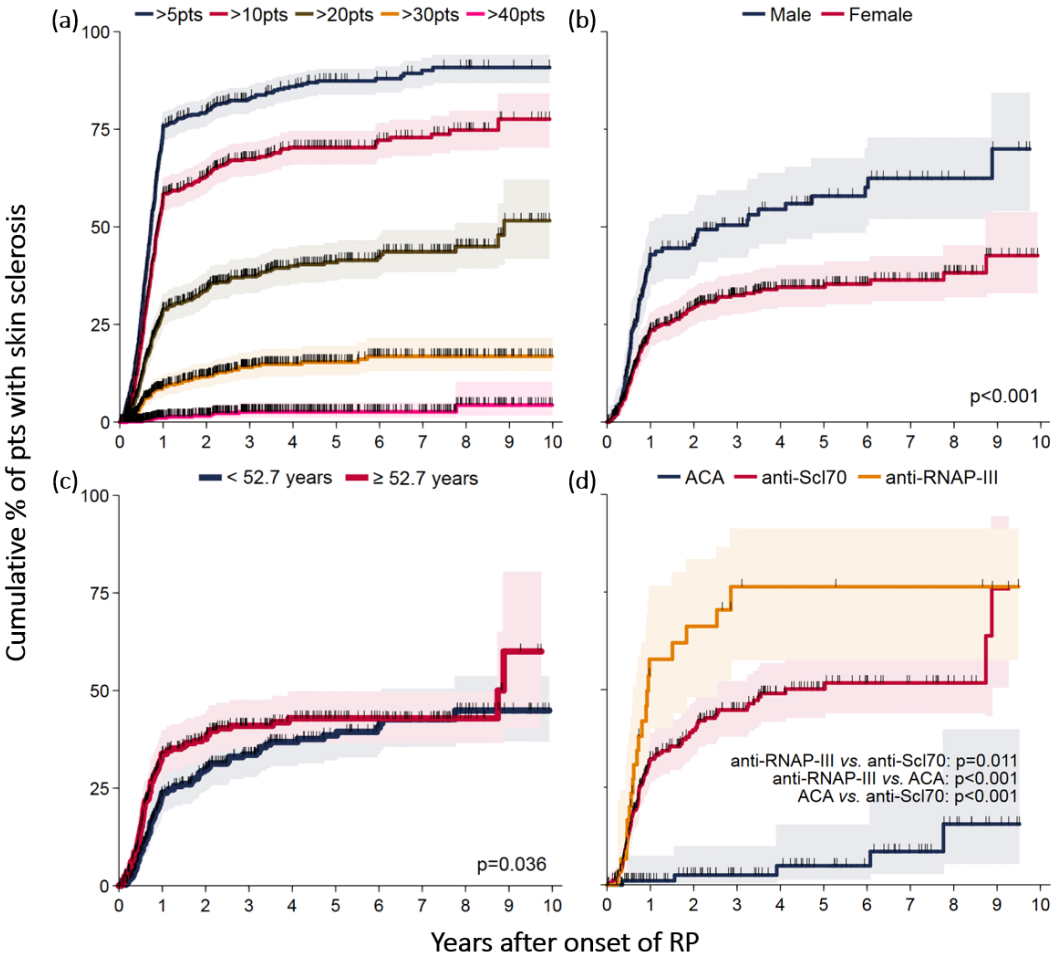
Figure 6. Time to peak mRSS. The histogram plots the percentage of patients as a function of the time to reach their maximal mRSS from RP onset; for all patients (a) and divided into patients with limited cutaneous involvement and diffuse cutaneous involvement (b).
The median peak mRSS was 15 points (IQR 7-24) overall, 9.5 points (IQR 6-14) in patients with limited cutaneous involvement and 23 points (IQR 16-29.5) in patients with diffuse cutaneous involvement.



Skin sclerosis by mRSS severity

Figure 7a shows the probabilities to develop a total mRSS above 5, 10, 20, 30 or 40 points. Only 1.2% of patients developed a total mRSS>40 points in the first year. In contrast, the probability of having ≤5 mRSS points was 24.1% (95%CI 20.7-27.6) in the first year.

Figure 7. Kaplan-Meier curves with 95%CI of patients developing a mRSS >5 points, >10 points, >20 points, >30 points and >40 points after the onset of RP (a). Developing a total mRSS >20 points was further stratified by sex (b), by the median age at the onset of RP (c), and by their autoantibody status (d).
Hash marks illustrate censored observations.



Men had an almost twofold higher rate than women to develop a mRSS>20 points (rate ratio 1.8, 95%CI 1.3-2.4) in the first year (Figure 7b). Moreover, age at disease onset was found to be a predictor for severe skin involvement (mRSS>20 points) early during the disease course. The probability to develop a mRSS>20 points within one year was higher in older patients than in younger subjects when dichotomised at the median age (52.7 years, Figure 7c). However, within the following 5 years the probabilities of both age groups to develop severe skin involvement converged to approximately 42%.

The analysis of the development of skin sclerosis by the presence of serum autoantibodies in the patients' sera revealed that all patients harbouring anti-RNAP-III autoantibodies and develop a total mRSS>20 points did so within 3 years after onset of RP (Figure 7d); the 3-year probability was 76.4% (95%CI 57.7-91.1). Patients with anti-Scl-70 autoantibodies also had a significantly higher probability of acquiring a mRSS>20 points in the first three years, than patients with ACA (44.8%, 95%CI 38.2-52.0 *vs*. 2.5%, 95%CI 0.6-9.7, respectively).

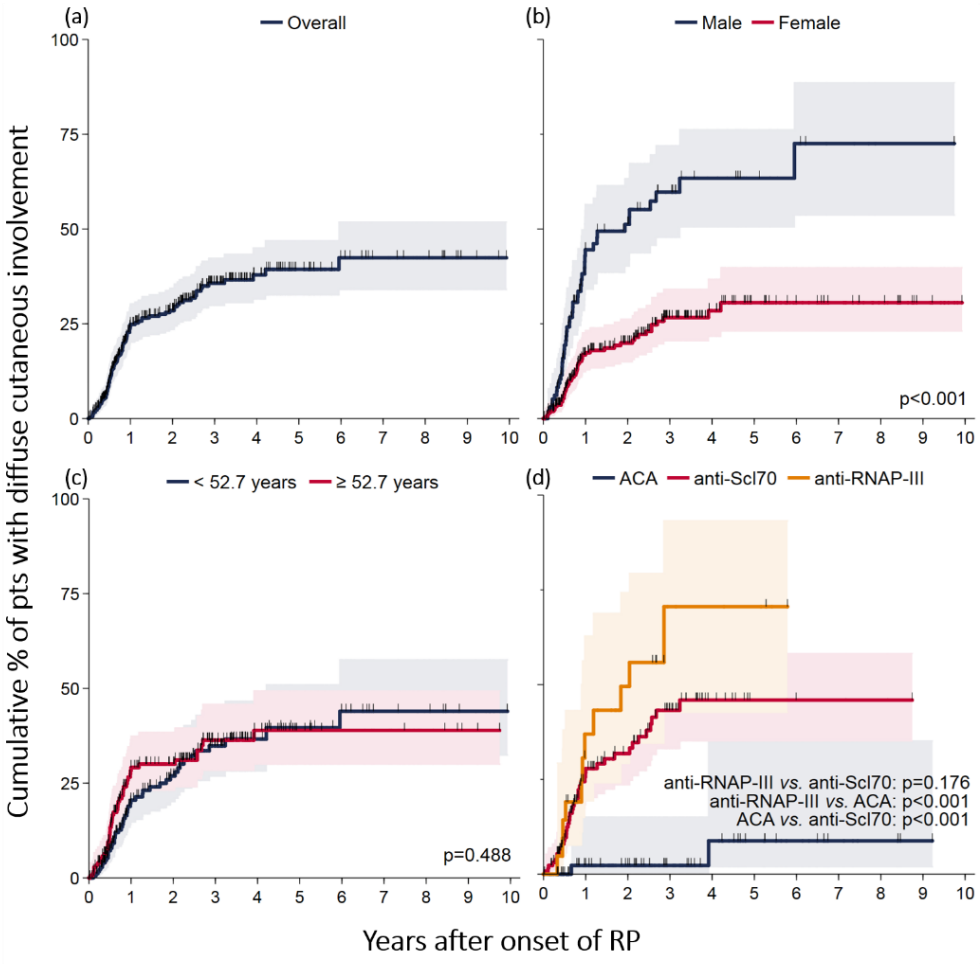
Diffuse cutaneous involvement

The probability to develop diffuse cutaneous involvement, defined as a mRSS≥2 at any area of the proximal extremities or trunk within the first year was 24.8% (95%CI 20.2-30.3) increasing to 35.7% (95%CI 29.9-42.3) during the subsequent two years (Figure 8a). Only a minority of patients developed a diffuse cutaneous involvement beyond three years after RP onset.

The rate of developing diffuse skin involvement in the first year in men was more than twice that in women (rate ratio 2.4, 95%CI 1.5-3.96; Figure 8b). There was however no evidence for differences in the probability of developing diffuse skin involvement between younger and older age groups (Figure 8c).

With respect to autoantibody status, the rates of developing diffuse cutaneous involvement in the first three years were highest in patients with anti-RNAP-III autoantibodies (70.6/100 patient years, 95%CI 42.7-93.2), followed by those with anti-Scl-70 autoantibodies (43.2/100 patient years, 95%CI 33.1-54.9), and lowest in patients with ACA (2.3/100 patient years, 95%CI 0.3-15.1; Figure 8d).

Figure 8. Kaplan-Meier curves with 95%CI of the first reported diffuse cutaneous involvement after the onset of RP in all patients in this analysis (a), stratified by sex (b), by the median age at the onset of RP (c), and by their autoantibody status (d).
Hash marks illustrate censored observations.

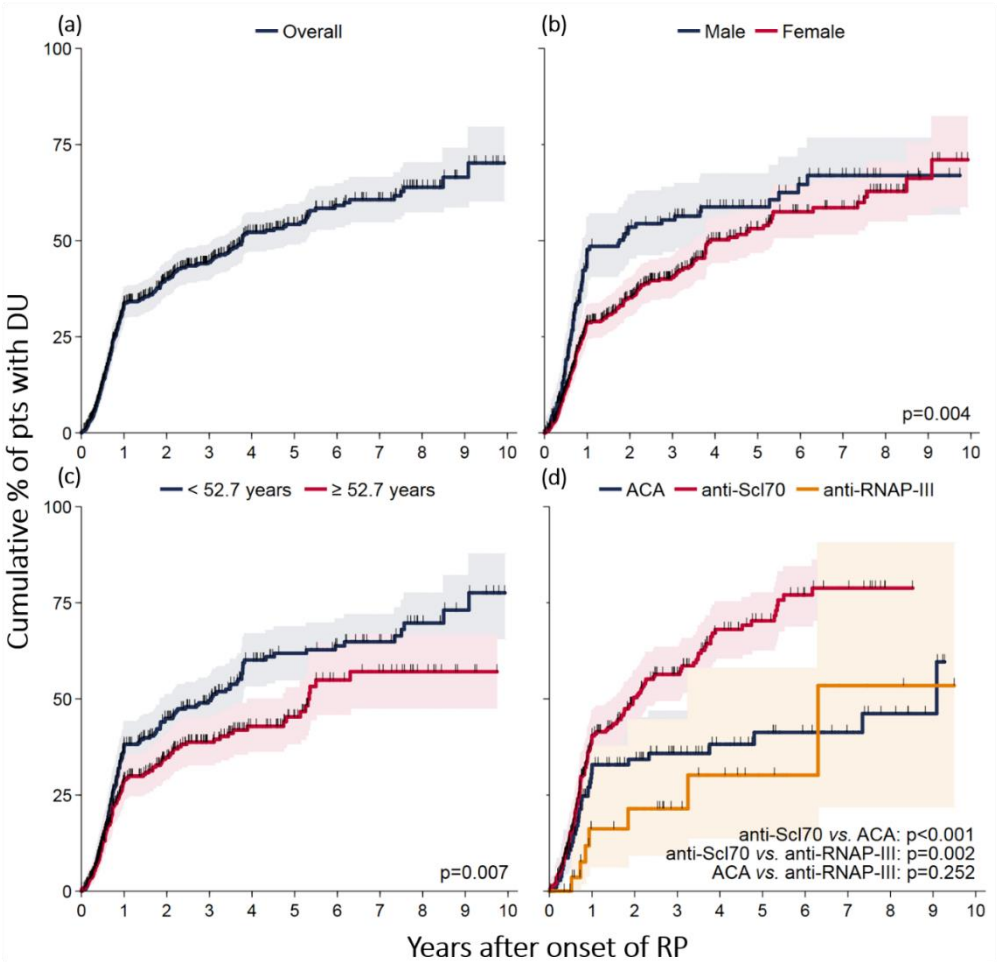


In the multivariable analysis of potential risk factors for the development of diffuse cutaneous involvement, defined as signs and symptoms present within the first year after RP onset, the presence of anti-RNAP-III and anti-Scl-70 autoantibodies conferred an elevated risk (HR 16.9, 95%CI 3.7-77.4 and 10.7, 95%CI 2.5-44.9) compared with ACA. Furthermore, male sex was also confirmed as a risk factor for diffuse cutaneous involvement (HR 2.7, 95%CI 1.6-4.7, supplementary). However, neither patient's age at RP onset nor the presence of DU or puffy fingers were associated with the development of diffuse cutaneous involvement.

Digital ulcers

There was a steep increase of DU development in the first year (**Figure 9a**), with a probability of 33.7% (95%CI 30.0-37.8). Unlike skin sclerosis, the probability of patients to develop DU increased continuously over the 10-year observational period to a maximum of 70.2% (95%CI 60.4-79.5) after the initial steep increase in the first year. The median time to DU development among those patients who acquired DU was short (0.7 years, IQR 0.4-1.7; mean 1.4 years, SD 1.6).

Figure 9. Kaplan-Meier curves with 95%CI of the observed first DU after the onset of RP (a), stratified by sex (b), by the median age at the onset of RP (c), and by their autoantibody status (d).
Hash marks illustrate censored observations.



Men had a significantly higher incidence rate of DU within the first year than women (66.5/100 patient years, 95%CI 53.0-83.6 *vs*. 42.0 patient years, 95%CI 35.2-50.1). After 6 years however, the probabilities to develop DU converged to approximately 60% in both sexes (**Figure 9b**).

Younger patients tended to be affected by DU earlier and more frequently, than older subjects (**Figure 9c**). In contrast to skin sclerosis, patients with anti-RNAP-III had a lower probability to develop DU than those with anti-Scl-70 autoantibodies (**Figure 9d**). Of note, there was no difference in the probability between patients with anti-RNAP-III autoantibodies and those with ACA. Only the presence of anti-Scl-70 autoantibodies was associated with DU development (HR 1.8, 95%CI 1.2-2.6) in multivariable analysis, but not the presence of the other autoantibodies, age at RP onset, sex or the presence of puffy fingers (**Supplementary Table 1**).

DISCUSSION

This study has analysed prospectively the incidence of SSc skin manifestations in patients who present as early as one year after the onset of RP. An important finding is that most patients acquire the maximal gain of skin sclerosis within 1 year after RP onset and that diffuse cutaneous involvement emerges newly in only a minority of patients after five years of disease onset. This study, in which we also map the evolution of skin sclerosis at different body areas, underlines, that the fibrotic process is most fulminant initially in all body areas, and less active at later stages. The study by Steen and Medsger also highlighted that a mRSS above 40 points mainly occurred in the first three years in patients with diffuse cutaneous SSc, but was not able to detail the evolution of skin sclerosis during the first three year period and to investigate the disease evolution in patients with a mRSS below 40 points [Steen *et al.*, 2000].

Our study confirmed that the presence of some autoantibodies is associated with the severity of skin sclerosis, as demonstrated in several cross-sectional studies [Kuwana *et al.*, 1993; Walker *et al.*, 2007; Nikpour *et al.*, 2011]. Although two small cross-sectional studies suggested an association between anti-RNAP-III autoantibodies and diffuse cutaneous involvement or a higher mRSS [Kuwana *et al.*, 1993; Nikpour *et al.*, 2011]. None of these studies compared several

autoantibodies simultaneously and none of these studies highlighted the effect of anti-RNAP-III positivity on the incidence and mRSS kinetics during the early disease course.

It is still a matter of debate as to whether patients with late-age onset SSc are more likely to have limited or diffuse cutaneous SSc than early-age onset SSc patients [Derk *et al.*, 2006; Hügle *et al.*, 2011; Manno *et al.*, 2011; Alba *et al.*, 2014]. Some investigators found no differences in the severity of skin involvement between age-of-onset groups [Weng *et al.*, 2010; Hügle *et al.*, 2011]. In line with a previously published cross-sectional analysis of our cohort, younger age at SSc onset was not associated with a higher mRSS in this longitudinal analysis [Walker *et al.*, 2007].

The short median time to mRSS peaking and the fact that the mRSS gain is highest in the first year of disease regardless of the magnitude of the maximal mRSS suggests that SSc kinetics peak within the first year in the skin despite inter-individual differences in the final severity of skin sclerosis. Interestingly, the risk factors governing the extent and severity of skin involvement (e.g. male sex and autoantibody status being associated with the development of diffuse disease), were not found to influence the disease kinetics (e.g. the time to mRSS peaking).

In contrast to the rapid initial evolution of skin sclerosis, the probability to develop DU increased more continuously over time. In our study, only the presence of anti-Scl-70, and not that of anti-RNAP-III autoantibodies, was associated with an increased incidence of DU, compared to the presence of ACA. These findings are in line with several previous studies that suggest a higher prevalence of DU in patients with anti-Scl-70 autoantibodies compared with patients without these autoantibodies [Walker *et al.*, 2007; Hanke *et al.*, 2009]. A small retrospective cohort also suggested that patients with anti-RNAP-III autoantibodies had less peripheral vascular disease than patients with anti-Scl-70 autoantibodies, and similar rates to patients with ACA [Vanthuyne *et al.*, 2012].

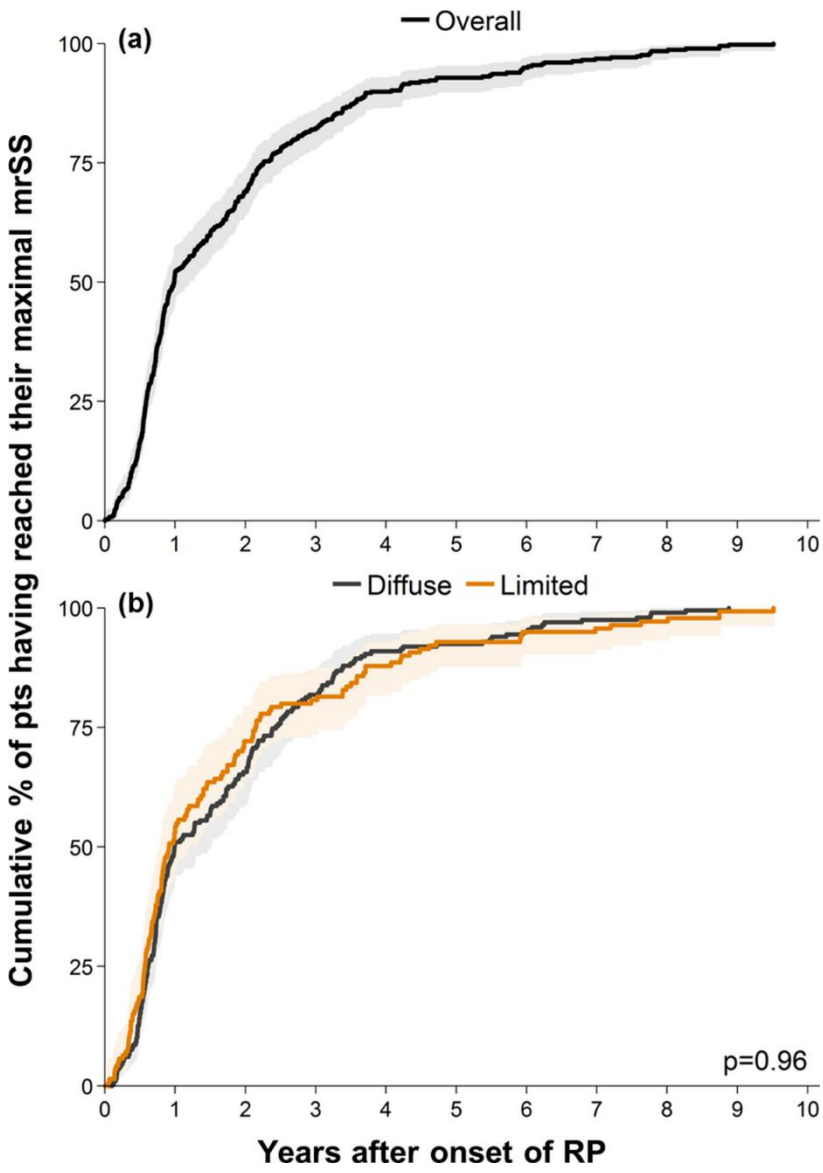
Most studies agree in the observation that DU are less prevalent in late-age than young-age onset patients [Walker *et al.*, 2007; Sunderkötter *et al.*, 2009; Hügle *et al.*, 2011; Khimdas *et al.*, 2011; Manno *et al.*, 2011; Alba *et al.*, 2014]. The univariable analysis of our prospective study also highlights a higher DU incidence in patients who are young at disease onset, but interestingly this association was lost after controlling for sex and autoantibody status.

The strengths of our investigation are the large sample size and the longitudinal multinational nature of our cohort. The mRSS score has been validated as a reliable outcome measure and demonstrated large effect sizes and sensitivity to change [Clements *et al.*, 1995; Kaldas *et al.*, 2009]. A somewhat smaller effect size must be taken into account when interpreting skin scores of isolated body sites and the mRSS inter-observer variability must be accounted for when interpreting cohort data. We also only analysed patients who had been recruited into EUSTAR within the first year after RP onset, thereby simulating an inception cohort. This selection and the fact that we only recruited patients who fulfilled the ACR classification criteria for SSc is however also a limitation of this study, as evidenced by the high prevalence of risk factors generally attributed to an adverse outcome (male sex and anti-Scl-70 positivity) in the patients included, as compared to those excluded [Perera *et al.*, 2007; Walker *et al.*, 2007; Elhai *et al.*, 2016]. As a consequence, the patients included had a comparatively higher median mRSS and more often diffuse cutaneous involvement at the baseline visit. Therefore, the results of our study must not be generalized to patients who present with SSc later than one year after RP onset. It should be also noted that the temporal evolution of skin manifestations might be underestimated, as some patients already had skin sclerosis at baseline. By including in this study only patients with a baseline visit within one year after RP onset, we tried to keep this effect low. In future studies, it may be interesting to follow patients who only meet the ACR/EULAR and not the ACR classification criteria for SSc and to study drug effects.

Our study nevertheless critically contributes to the management of those SSc patients who present early after RP onset. By mapping the temporal evolution of skin sclerosis and DU and identifying risk factors early during the disease course, our findings will enable physicians to more accurately counsel SSc patients presenting early. The long-term prospective data on the large number of EUSTAR patients presented here will facilitate the design of clinical trials aiming to prevent disease evolution as well as those evaluating new diagnostic tests and therapeutic strategies.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Kaplan-Meier curves with 95%CI of the time to reach the maximal mRSS after the onset of RP in all patients in this analysis (a) and divided into patients with limited cutaneous involvement and diffuse cutaneous involvement (b).



Supplementary Table 1. Cox multivariable regression analysis of factors associated with the time to reach the mRSS peak, to develop diffuse cutaneous involvement and to develop DU.

	mRSS peak		Diffuse cutaneous involvement		Digital ulcers	
	HR	95%CI	HR	95%CI	HR	95%CI
Sex						
Female	1		1		1	
Male	1.26	0.85-1.86	2.72	1.57-4.73	1.23	0.90-1.68
Age at onset of RP (years)	1.01	0.99-1.02	1.01	0.99-1.03	0.99	0.98-1.00
Autoantibody status						
ACA	1		1		1	
Anti-Scl-70	1.02	0.67-1.57	10.67	2.54-44.85	1.75	1.20-2.56
Anti-RNAP-III	1.07	0.53-2.13	16.93	3.70-77.40	0.58	0.26-1.32

ARTICLE 2: INCIDENCES AND RISK FACTORS OF ORGAN MANIFESTATIONS IN THE EARLY COURSE OF SYSTEMIC SCLEROSIS: A LONGITUDINAL EUSTAR STUDY.

Veronika K. Jaeger[1], Elina G. Wirz[1,2], Yannick Allanore[3], Philipp Rossbach[1], Gabriela Riemekasten[4], Eric Hachulla[5], Oliver Distler[6], Paolo Airò[7], Patricia E. Carreira[8], Alexandra Balbir Gurman[9], Mohammed Tikly[10], Serena Vettori[11], Nemanja Damjanov[12], Ulf Müller-Ladner[13], Jörg H. W. Distler[14], Mangtao Li[15], Ulrich A. Walker[1*] on behalf of EUSTAR co-authors[^]

[1] Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[2] Department of Dermatology, University Hospital Basel, Basel, Switzerland
[3] Department of Rheumatology A, Cochin Hospital, Paris Descartes University, Paris, France
[4] Department of Rheumatology, University Clinic Schleswig-Holstein, Lübeck, Germany
[5] Service de Médecine Interne, Hôpital Huriez, Université de Lille, Lille, France
[6] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[7] UO Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italy
[8] Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain
[9] B. Shine Rheumatology Unit, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion - Institute of Technology, Haifa, Israel
[10] Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa
[11] Rheumatology Department, Second University of Naples, Naples, Italy
[12] Institute of Rheumatology, University of Belgrade Medical School, Belgrade, Serbia
[13] Department of Rheumatology and Clinical Immunology, Kerckhoff Clinic, Justus-Liebig University Giessen, Bad Nauheim, Germany
[14] Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany
[15] Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

EUSTAR CO-AUTHORS:

Lidia Ananieva; Stefan Heitmann; Simona Rednic; Sergio Jimenez; Valeria Riccieri; Magdalena Szmyrka-Kaczmarek; Dominique Farge; Giovanni Lapadula; Marco Matucci-Cerinic; Serena Guiducci; Nicolas Hunzelmann; Maria Rosa Pozzi; Carina Mihai; Douglas Veale; Roger Hesselstrand; Eduardo Mariok; Vanessa Smith; Eugene J Kucharz; László Czirják; Duska Martinovic; Kamal Solanki; Codrina Mihaela Ancuta; Jean Sibilia; Caramaschi Paola; Manal

Hassanien; Sarah Kahl; Adrianne Woods; Marie Vanthuyne; Ionescu Ruxandra; Sebastião C. Radominski; Andrea Lo Monaco; Ada Corrado; Michaela Koehm; Montecucco Maurizio; Bevcar Radim; Esthela Loyo; Maria Üprus; Raffaele Pellerito; Thierry Zenone; Armando Gabrielli; Otylia Kowal-Bielecka; Blaz Rozman; Raffaella Scorza; Lesley Ann Saketkoo; Oyvind Midtvedt; Carlos Alberto von Mühlen; Jörg Henes; Ani Branimir; Paul Hasler; Sule Yavuz; Peter Villiger; Brigitte Krummel-Lorenz; Magdalena Posa; Merete Engelhart; Christopher Denton; Dorota Krasowska; Paloma Garcia de la Peña Lefebvre; Franco Cozzi; Luc Mouthon; Sergio Jimenez; Edoardo Rosato; Selmi Carlo; Juan José Alegre Sancho; Carmel Mallia; Massimiliano Limonta; Matthias Seidel; Rosario Foti; Lisa Stamp; Susanne Ullman; Simon Stebbings; Vera Ortiz Santamaria; Francesco Del Galdo; Ellen De Langhe; Alessandro Mathieu; Cord Sunderkötter; Kilian Eyerich; Bojana Stamenkovic; Srdan Novak; Percival D. Sampaio-Barros; Cristiane Kayser; Ira Litinsky; Maura Couto

CORRESPONDING AUTHOR: Ulrich A Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland; Phone: +41 61 32 87479; Fax: +41 61 26 59021; E-mail: ulrich.walker@usb.ch

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COMPETING INTERESTS: The authors have declared that no competing interests exist.

ETHICS APPROVAL: Ethics approval according to the Declaration of Helsinki has been obtained from all respective contributing centres' local ethics committees and ethics committee approval for the EUSTAR study was obtained from the Ethik Kommission Beider Basel (EKBB, now Ethikkommission Nordwest- und Zentralschweiz, EKNZ).

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CONTRIBUTORSHIP: Conceptualization: VKJ, UAW; Data curation: VKJ, EGW, UAW; Formal analysis: VKJ, EGW, UAW; Investigation: VKJ, EGW, YA, PR, GR, EH, OD, PA, PEC, ABG, MT, SV, ND, UML, JHWD, ML, UAW; Methodology: VKJ, EGW, UAW; Project administration: VKJ, UAW; Supervision: UAW; Visualization: VKJ, UAW; Writing – original draft: VKJ, UAW; Writing – review & editing: VKJ, EGW, YA, PR, GR, EH, OD, PA, PEC, ABG, MT, SV, ND, UML, JHWD, ML, UAW.

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ABSTRACT

Objective

SSc is a rare and clinically heterogeneous autoimmune disorder characterised by fibrosis and microvascular obliteration of the skin and internal organs. Organ involvement mostly manifests after a variable period of the onset of RP. We aimed to map the incidence and predictors of pulmonary, cardiac, GI and renal involvement in the early course of SSc.

Methods

In the EUSTAR cohort, patients with early SSc were identified as those who had a visit within the first year after RP onset. Incident SSc organ manifestations and their risk factors were assessed using Kaplan-Meier methods and Cox regression analysis.

Results

Of the 695 SSc patients who had a baseline visit within 1 year after RP onset, the incident non-RP manifestations (in order of frequency) were: skin sclerosis (75%) GI symptoms (71%), impaired diffusing capacity for monoxide<80% predicted (65%), DU (34%), cardiac involvement (32%), FVC<80% predicted (31%), increased PAPsys>40mmHg (14%), and renal crisis (3%). In the heart, incidence rates were highest for diastolic dysfunction, followed by conduction blocks and pericardial effusion.

While the main baseline risk factor for a short timespan to develop FVC impairment was diffuse skin involvement, for PAPsys>40mmHg it was higher patient age. The main risk factors for incident cardiac manifestations were anti-Scl-70 autoantibody positivity and older age. Male sex, anti-RNAP-III positivity, and older age were risk factors associated with incident renal crisis.

Conclusion

In SSc patients presenting early after RP onset, approximately half of all incident organ manifestations occur within 2 years and have a simultaneous rather than a sequential onset. These findings have implications for the design of new diagnostic and therapeutic strategies aimed to ‘widen' the still very narrow ‘window of opportunity'. They may also enable physicians to counsel and manage patients presenting early in the course of SSc more accurately.

INTRODUCTION

SSc is a rare and clinically heterogeneous autoimmune disorder. Prevalence estimates vary around 20 per 100'000 [Mayes, 2003]. The connective tissue and small vessels are mostly affected which leads to the characteristic fibrosis and vascular obliteration of the skin and internal organs, particularly of the heart, lungs, kidneys and digestive tract [Rodnan *et al.*, 1979; Gabrielli *et al.*, 2009]. In the vast majority of individuals, SSc starts with the onset of RP. Skin sclerosis and internal organ involvement manifest mostly either with a variable temporal interval after RP onset or simultaneously with RP.

Numerous cross-sectional studies have already assessed the prevalence of internal organ manifestations and calculated risk factors in patients with established SSc [Walker *et al.*, 2007; Allanore *et al.*, 2010; Hügle *et al.*, 2011; Manno *et al.*, 2011; Hasegawa *et al.*, 2013; Alba *et al.*, 2014]. These studies have demonstrated that the presence of specific autoantibodies in the patient's serum, the patient's sex, and age at SSc onset as well as the extent of skin involvement are associated with the prevalence and severity of internal organ involvement [Walker *et al.*, 2007; Allanore *et al.*, 2010; Assassi *et al.*, 2010; Hügle *et al.*, 2011; Manno *et al.*, 2011; Hasegawa *et al.*, 2013; Alba *et al.*, 2014; Avouac *et al.*, 2016; Elhai *et al.*, 2016].

As internal organ involvement constitutes an important cause of morbidity and mortality, exact data about the incidence and temporal evolution of their manifestation after RP onset are essential for physicians, who need to counsel patients and risk stratify them early after SSc diagnosis; and for investigators, who design and perform a clinical trial aimed at altering the natural course of SSc [Kahan *et al.*, 2006; Steen *et al.*, 2007; Omair *et al.*, 2012]. However, only few studies have prospectively assessed the evolution of SSc-related organ manifestations after the onset of RP. Given the paucity of reliable data, our aim was to map the incidence of internal organ manifestations early during the course of disease. By using real-life data from the large and multinational EUSTAR cohort [Walker *et al.*, 2007; Meier *et al.*, 2012], we assessed the acquisition of pulmonary, cardiac, gastrointestinal or renal involvement in patients who developed SSc no later than 1 year after RP onset.

PATIENTS AND METHODS

Study population and design

The structure of the multicentre and international, prospective, longitudinal EUSTAR database has been described previously [Walker *et al.*, 2007; Meier *et al.*, 2012]. Ethics approval according to the Declaration of Helsinki has been obtained from all respective contributing centers' local ethics committees and ethics committee approval for the EUSTAR study was obtained from the Ethik Kommission Beider Basel (now Ethikkommission Nordwest- und Zentralschweiz). Each participating centre obtained local ethics committee approval and written informed consent was required to be signed by each patient. Demographic and disease characteristics were collected between the time of the database implementation in 2004 and February 2014. Data were considered for analysis on the condition that patients were older than 18 years at the time of the visit, and fulfilled the 1980 American College of Rheumatology (ACR) classification for SSc [Masi *et al.*, 1980]. This dataset is hereafter called the '*entire EUSTAR cohort*'. In a second filtering step, the study population was further restricted to patients who had a baseline visit within the first year after RP onset, in order to ensure that patients were enrolled early in their disease course. This restricted dataset is hereafter called '*the study population*'.

Study outcomes

In the *entire EUSTAR cohort*, the time between RP onset and the onset of the first non-RP manifestation of SSc was evaluated. In the restricted *study population*, the time between RP onset and the onset of various organ manifestations was assessed i.e. skin involvement (defined as a mRSS ≥2 points in at least 1 body area); GI symptoms (defined as the patient reporting either dysphagia, reflux, early satiety, vomiting, diarrhoea, bloating or constipation); a PAPsys >40 mmHg as a proxy for suspected pulmonary hypertension; FVC <80% of predicted as a proxy for a pulmonary restrictive defect; DU; cardiac involvement (defined as either the presence of diastolic dysfunction, conduction blocks, LVEF <50%, or a pericardial effusion); and lastly, renal crisis and erectile dysfunction (defined as a score <22 points in the IIEF-5 questionnaire) [Rosen et al., 1997]. Table 3 summarises the EUSTAR definitions of the study outcomes assessed.

Table 3. Definitions of study outcomes

Study outcome	Description
Skin involvement	A modified Rodnan skin score of 2 or more points in at least 1 body area.
Gastrointestinal symptoms	Any of dysphagia, reflux, early satiety, vomiting, diarrhoea, bloating and/or constipation as reported by the patient.
Elevated systolic pulmonary artery pressure	A systolic pulmonary artery pressure as estimated by echocardiography of more than 40 mmHg as a proxy for suspected pulmonary hypertension.
Impaired forced vital capacity	A forced vital capacity of less than 80% of predicted as a proxy for a pulmonary restrictive defect.
Digital ulcers	Current ulcers distal to or at the proximal interphalangeal joint not thought to be due to trauma.
Cardiac involvement	Any of diastolic dysfunction, conduction blocks, impaired left ventricular ejection fraction and/or pericardial effusion.
Diastolic dysfunction	As estimated by echocardiography.
Conduction blocks	Atrioventricular block, bundle branch blocks as assessed by electrocardiography.
Impaired left ventricular ejection fraction	A left ventricular ejection fraction less than 50% as estimated by echocardiography.
Pericardial effusion	A pericardial effusion of 5mm or more as estimated by echocardiography.
Renal crisis	Scleroderma renal crisis as per scleroderma expert judgement.
Erectile dysfunction	A score of less than 22 points in the International Index of Erectile Function questionnaire [Rosen *et al.*, 1997].

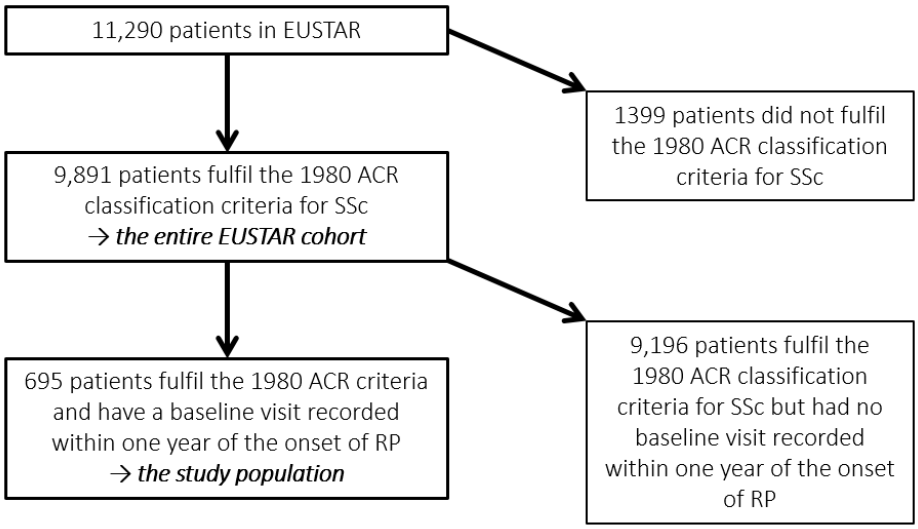
Statistical analysis

Frequencies and percentages as well as medians and IQR and means and SD were reported for categorical and continuous variables, respectively. Kaplan-Meier analyses were carried out to assess the cumulative probabilities of developing disease features as a function of time after RP onset for cases with available information. The date of the visit at which organ manifestations were first observed was used as the end time, i.e. the incidence. As the first visit was required to be within the first year after RP onset, manifestations that were already present at the first visit were also regarded as incident. If the manifestation was never observed, the date of the last follow-up visit was set as the censor time. Kaplan-Meier estimates were

stratified by sex, age (dichotomized at the median age at RP onset), autoantibody status, and diffuse or limited skin involvement. Patients were classified as having diffuse or limited skin involvement according to their skin involvement with the first year after RP onset. Strata were compared with log-rank tests. Furthermore, incidence rates and their 95% CI were calculated. Cox proportional hazards regression analysis was used to assess the combined effect of the potential risk factors sex, age, autoantibody status and the extent of skin involvement on disease manifestations. All data were analysed with Stata 13.1 (Stata Corporation, College Station, Texas, USA).

RESULTS

Figure 10. Flow chart of patients included and excluded in the analysis.



Patient characteristics

At the time of censoring, a total of 11,290 patients were followed in the EUSTAR database. Of these patients, 9,891 adult patients fulfilled the 1980 ACR classification criteria for SSc, and were therefore included in the subsequent analysis of the entire EUSTAR cohort [Masi *et al.*, 1980]. The study population, consisting of patients with a baseline visit within the first year

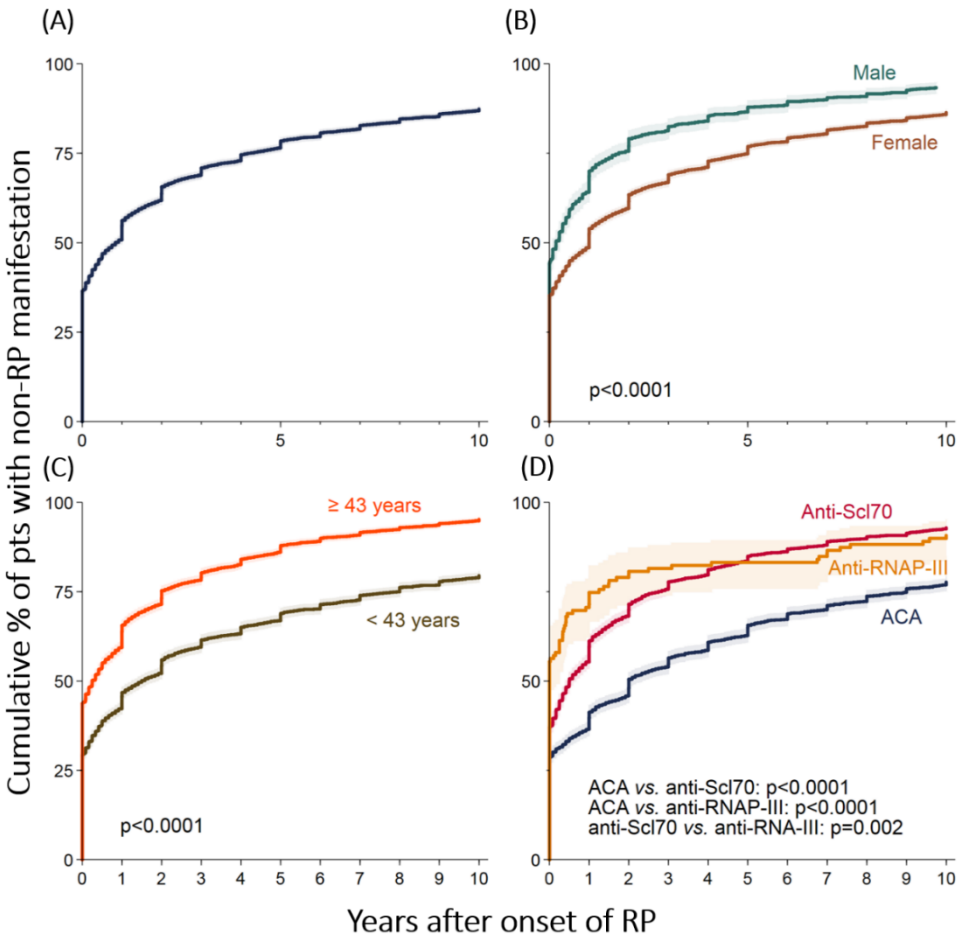
after RP onset, was composed of 695 subjects (**Figure 10**) with a median observation time of 2.1 years (IQR 0.7-4.6; mean 3.1 years, SD 3.0). The median age of the study population was 52.7 years (IQR 42.3-62.5) at RP onset, 27% were men (**Table 4**).

The other patients followed in the entire EUSTAR cohort were on average about 9 years older and about 13% of these were male (**Table 4**). Compared to the study population, a higher percentage of the other patients followed in the *entire EUSTAR cohort* was ACA positive and a lower percentage had anti-Scl-70 or anti-RNAP-III autoantibodies (**Table 4**).

Table 4. Comparison of disease characteristics at the baseline visit between patients included in this analysis (visit within 1 year after onset of RP, study population) and those excluded (no visit within 1 year after onset of RP).
* Data were only captured by EUSTAR since 2007; # Number of patients with available information for each variable.

Patient characteristics at baseline visit	n#	Included	Excluded	P-Value
Number of patients	695	695	9196	
Age at onset of RP, years; mean (SD)	695	51.7 (14.2)	42.4 (14.8)	<0.001
Male, %	695	26.6	13.3	<0.001
Laboratory parameters per patient				
ANA, %	683	96.1	96.4	0.67
ACA, %	648	16.7	34.7	<0.001
Anti-Scl-70, %	659	42.0	33.2	<0.001
Anti-RNAP-III*, %	317	9.5	2.9	<0.001
Disease characteristics at baseline				
Age at onset of first non-RP, years; mean (SD)	607	50.9 (14.4)	46.3 (14.1)	<0.001
Digital ulcers, %	684	28.4	34.2	0.002
Puffy fingers*, %	375	52.7	37.3	<0.001
mRSS; median (IQR)	643	10.0 (4.0-19.0)	6 (3.0-12.0)	<0.001
Diffuse cutaneous involvement*, %	327	20.6	9.0	<0.001
FVC*, % of predicted; mean (SD)	294	90.3 (19.3)	93.5 (21.4)	0.01
DLCO, % of predicted; mean (SD)	500	68.9 (20.8)	68.9 (20.6)	0.99
PAPsys*, mmHg; mean (SD)	242	30.2 (12.3)	30.6 (13.2)	0.63
Diastolic dysfunction, %	621	15.0	17.7	0.08
Conduction blocks, %	629	8.9	10.7	0.15
Left ventricular ejection fraction*, %; mean (SD)	284	62.8 (6.4)	62.1 (6.7)	0.12
Pericardial effusion*, %	286	8.4	6.0	0.11
Oesophageal symptoms, %	692	56.7	66.2	<0.001
Stomach symptoms, %	686	19.2	24.4	0.003
Intestinal symptoms, %	688	16.9	24.5	<0.001
Renal crisis, %	687	2.6	2.0	0.28

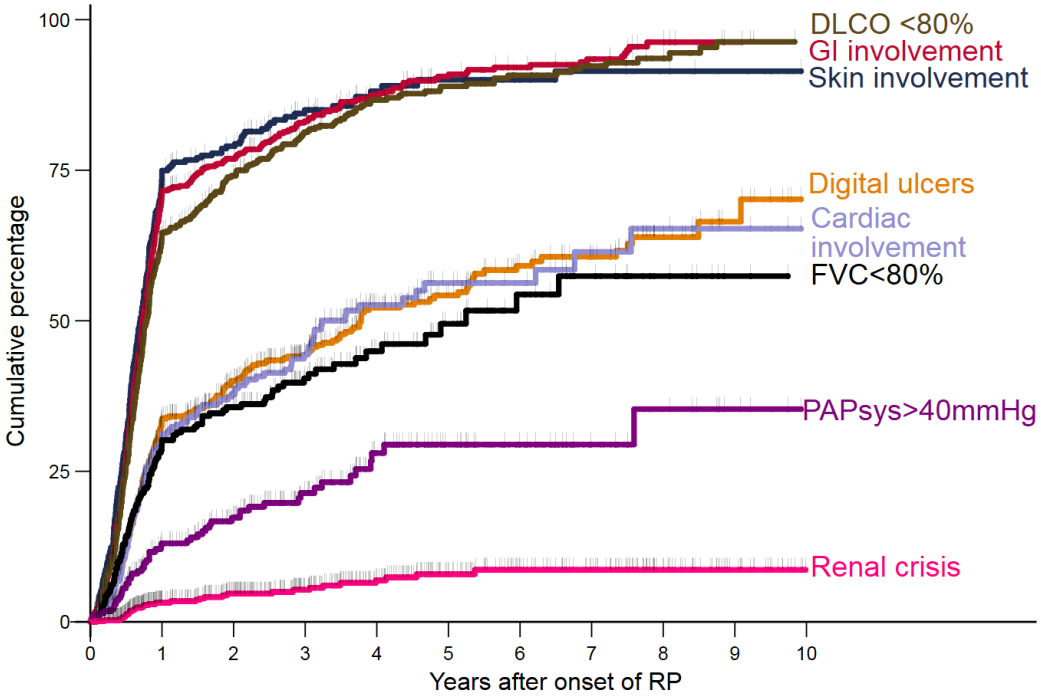
Figure 11. Kaplan-Meier curves with 95% CI of the manifestation of any first non-RP feature after RP onset in all SSc patients in the entire EUSTAR cohort (A) and stratified by sex (B), the median age at RP onset (C) and the autoantibody status (D).



Evolution of first non-RP manifestation of SSc in the entire EUSTAR cohort

In the *entire EUSTAR cohort* around 87% of patients had their first non-RP feature of the disease either after RP onset, or simultaneously with RP onset. The median time from RP onset until the first non-RP manifestation of SSc was 0.9 years (IQR 0-4.2), with 90% of patients acquiring their first non-RP manifestation within 12.0 years (95%CI 89.5-90.8; **Figure 11A**). Men developed the first non-RP manifestation faster than women (**Figure 11B**), and older patients were affected faster than younger patients (**Figure 11C**). Patients with anti-RNAP-III and anti-Scl-70 autoantibodies were more likely to develop a non-RP manifestation faster than patients with ACA (**Figure 11D**). A multivariable analysis confirmed the aforementioned risk factors for disease onset (data not shown).

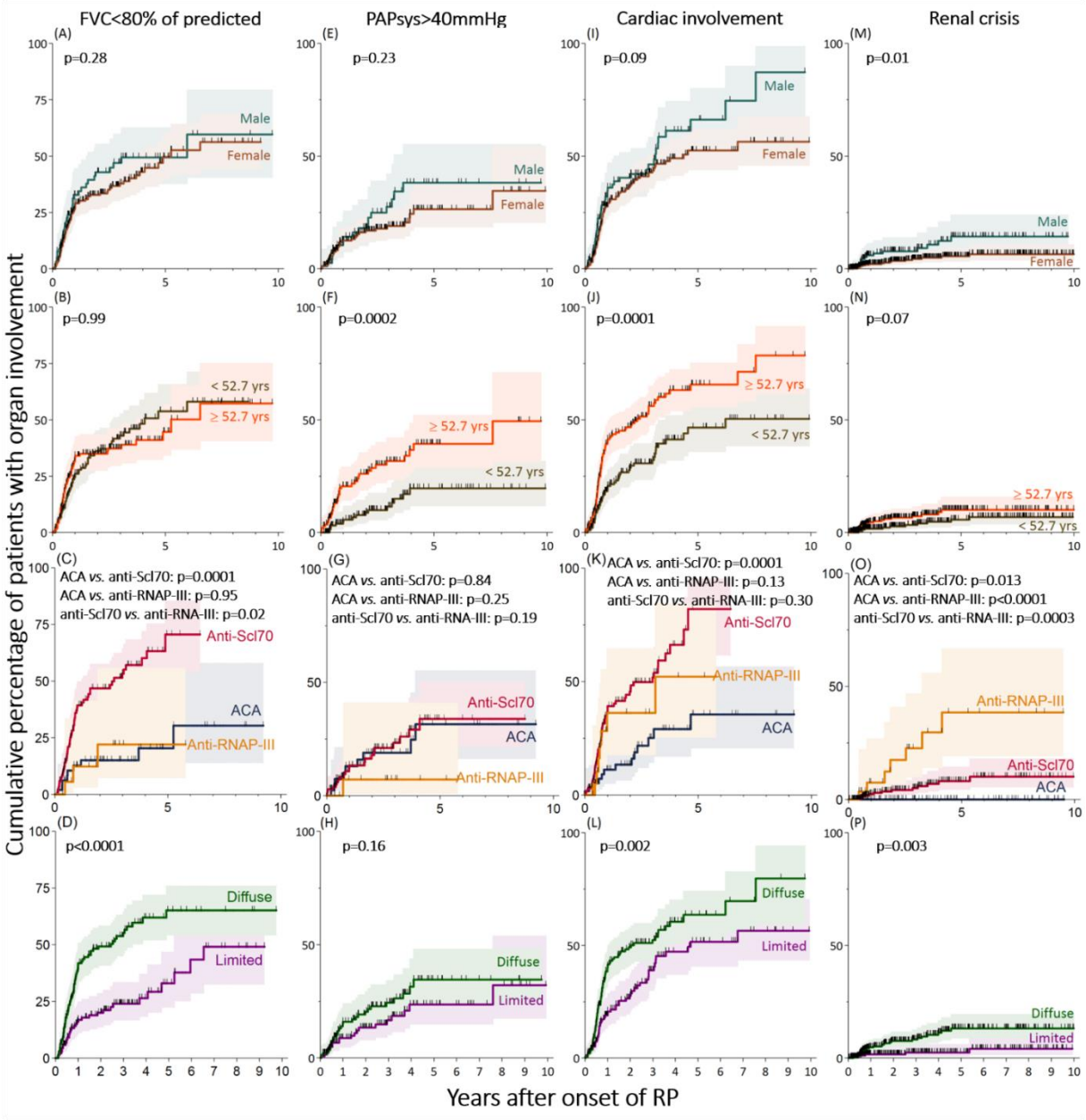
Figure 12. Kaplan-Meier curves of incident organ involvement in SSc patients of the study population after RP onset.
Hash marks represent censored observations.



Evolution of any organ involvement in the study population

Among *the study population*, the probability of developing any organ involvement varied among the different organ systems (**Figure 12**). More than 90% of patients in the study population developed either a skin involvement, GI symptoms, or a single breath diffusing capacity for monoxide (DLCO)<80% of predicted, the majority of patients within the first year. The incidence rates of DU, cardiac involvement and FVC<80% of predicted were considerably lower; PAPsys>40 mmHg and renal crisis were least frequent.

Figure 13. Kaplan-Meier curves with 95% CI of incident pulmonary restriction (FVC<80% of predicted; (A-D)), suspected pulmonary hypertension (PAPsys>40 mmHg; (E-H)), cardiac involvement (I-L) and renal crisis (M-P) after RP onset in SSc patients of the study population; stratified by sex (A/E/I/M), the median age at RP onset (B/F/J/N), autoantibody status (C/G/K/O) and extent of skin involvement within the first year after RP onset (D/H/L/P).
Hash marks represent censored observations.



Pulmonary complications

There was no evidence that the frequency and the time to develop a FVC<80% of predicted were influenced by the patient's sex and age (**Figure 13A** and **Figure 13B**). There were however differences according to the serum autoantibody status (**Figure 13C**) as patients harbouring anti-Scl-70 autoantibodies had a significantly higher incidence of FVC<80% of predicted than patients with anti-RNAP-III autoantibodies (incidence ratio 3.6, 95%CI 1.2-17.9), and with ACA (incidence ratio 4.7, 95%CI 2.3-10.7). Patients with diffuse skin involvement within the first year after RP onset also more frequently had a FVC<80% of predicted than patients with limited skin involvement (incidence ratio 2.8, 95%CI 1.8-4.3; **Figure 13D**). In multivariable analysis, diffuse skin involvement within the first year after RP onset was the only significant risk factor for incident FVC<80% of predicted (**Table 5**).

A FVC<50% of predicted (i.e. a severe pulmonary restrictive defect) was diagnosed in 2% (95%CI 1-5) of patients within the first year and in 12% (95%CI 6-23) during the 10-year follow-up.

The probability to develop a DLCO<80% of predicted was high (**Figure 12**). In multivariable analysis, anti-Scl-70 positivity as well as a diffuse skin involvement were the main risk factors for incident DLCO<80% of predicted (HR 1.60, 95%CI 1.12-2.28; HR 1.52, 95%CI 1.14-2.02, respectively).

In the first 3 years after RP onset, about one third of patients acquired a DLCO<50% of predicted (95%CI 27-36), with a progressive increase to 54% of patients (95%CI 44-65) during the observational period. Older patients, male patients, patients with anti-Scl-70 autoantibodies, or with diffuse skin involvement had a higher incidence of DLCO<50% of predicted (incidence ratios: older *vs.* younger 1.8, 95%CI 1.3-2.5; male *vs.* female 1.9, 95%CI 1.4-2.6; anti-Scl-70 *vs.* ACA 3.6, 95%CI 2.0-6.49 diffuse *vs.* limited 2.9, 95%CI 2.0-4.2). However, only older age, the presence of anti-Scl-70 autoantibodies and diffuse skin involvement were confirmed risk factors for developing a DLCO<50% of predicted in multivariable analysis (HR 1.03 per 1 year increase of age, 95%CI 1.01-1.04; HR 2.64, 95%CI 1.23-5.64; HR 2.06, 95%CI 1.19-3.56, respectively).

The time to develop a PAPsys>40 mmHg was not associated with the patient's sex or the patient's extent of skin involvement (**Figure 13E** and **Figure 13H**). Older patients however acquired a PAPsys>40 mmHg faster and more frequently than younger patients (**Figure 13F**).

Patients with anti-RNAP-III autoantibodies showed a PAPsys>40 mmHg less frequently than patients harbouring ACA or anti-Scl-70 autoantibodies, but there was no statistically significant difference (Figure 13G). Patient's older age was confirmed to be the main risk factor for developing PAPsys>40 mmHg (Table 5).

Table 5. Cox multivariable regression analysis of risk factors for the time to incident FVC<80% of predicted, PAPsys>40 mmHg, any cardiac dysfunction, diastolic dysfunction, conduction block, pericardial effusion and renal crisis.

* no patient with ACA developed a renal crisis or pericardial effusion.

	FVC<80% of predicted		PAPsys >40mmHg		Any cardiac involvement		Diastolic dysfunction		Conduction block		Pericardial effusion		Renal Crisis	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Sex														
Male	1		1		1		1		1		1		1	
Female	1.30	0.75-2.25	**0.40**	**0.17-0.93**	0.85	0.52-1.38	1.09	0.54-2.22	2.12	0.85-5.28	0.46	0.19-1.13	**0.39**	**0.15-0.97**
Age at onset of RP (in years)	1.01	0.99-1.03	**1.09**	**1.05-1.13**	**1.04**	**1.02-1.06**	**1.08**	**1.04-1.11**	1.01	0.99-1.04	1.02	0.98-1.06	**1.04**	**1.00-1.08**
Autoantibody status														
ACA	1		1		1		1		1		-*	-	-*	-
Anti-Scl-70	2.37	0.80-7.03	2.04	0.61-6.80	**3.90**	**1.82-8.35**	1.78	0.61-5.20	17.59	3.81-81.33	1		1	
Anti-RNAP-III	0.62	0.13-2.91	0.49	0.05-4.76	2.56	0.91-7.19	2.09	0.55-8.00	6.62	0.88-49.95	0.31	0.04-2.31	**5.18**	**2.03-13.22**
Extent of skin involvement														
Limited	1		1		1		1		1		1		1	
Diffuse	**3.08**	**1.43-6.62**	0.91	0.33-2.50	0.93	0.52-1.64	1.78	0.72-4.38	**0.45**	**0.21-0.95**	2.86	0.65-12.51	2.96	0.68-12.81

Cardiac involvement

There was no evidence that a patient's sex was associated with the time to cardiac involvement (Figure 13L). Older patients, however, had a 2.1-fold higher incidence (95%CI 1.5-3.0; Figure 13J) and patients with diffuse skin involvement had a 1.9-fold higher incidence (95%CI 1.3-2.7) of cardiac involvement than patients with limited skin involvement (Figure 13L). Patients with anti-Scl-70 autoantibodies developed cardiac involvement more frequently and more rapidly than patients with ACA (incidence ratio 3.7, 95%CI 2.0-7.4; Figure 13K). In multivariable analysis older age and the presence of anti-Scl-70 autoantibodies remained risk factors for any cardiac involvement (HR 1.04 per 1 year increase of age and 3.90, respectively; Table 5).

The most common manifestation of cardiac involvement was diastolic dysfunction (Figure 14). The incidence of diastolic dysfunction did not differ between sexes and autoantibody status (incidence ratios: male vs. female 1.0, 95%CI 0.6-1.6; ACA vs. anti-Scl-70 0.5, 95%CI 0.2-1.1; ACA vs. anti-RNAP-III 0.5, 95%CI 0.2-1.8); though the incidence of diastolic dysfunction was 3.5 times (95%CI 2.1-5.9) higher in older than in younger patients. The frequency and the time to develop a diastolic dysfunction were also influenced by the extent of skin involvement with diffuse patients having a 2.1-fold higher incidence (95%CI 1.3-3.4). In the multivariable analysis, however, only older age remained a risk factor for diastolic dysfunction (HR 1.08 per 1 year increase of age; Table 5).

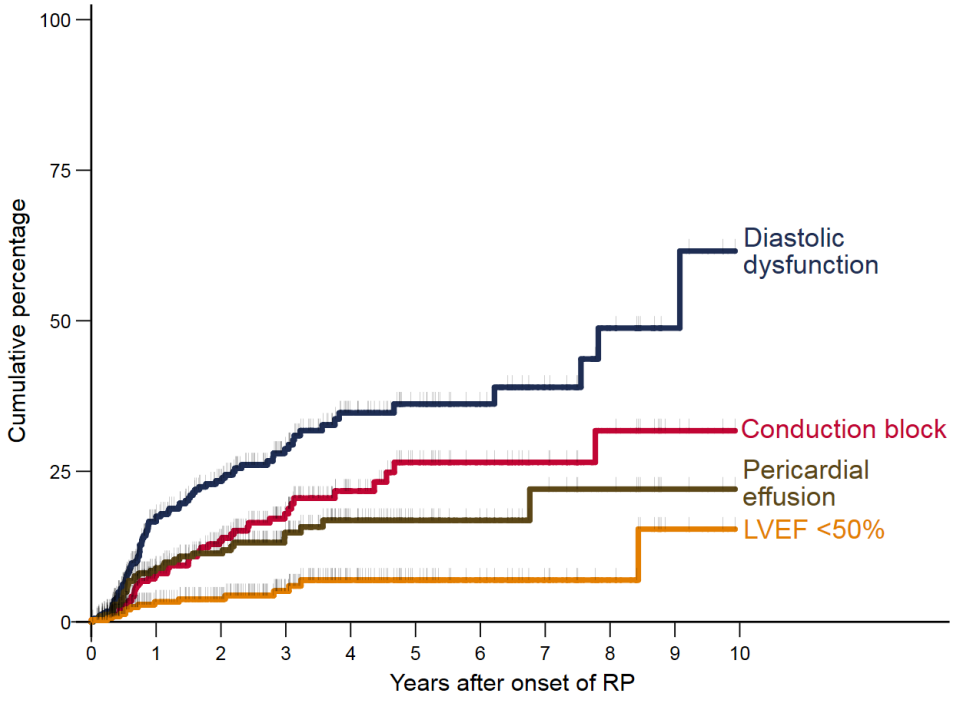
Conduction blocks were the second most frequent type of heart involvement (Figure 14). The incidence did neither vary by patient's sex, patient's age, nor the patient's extent of skin involvement; but patients with anti-Scl-70 autoantibodies had a considerably higher incidence of conduction blocks than patients with ACA (incidence ratio 10.0, 95%CI 2.5-86.2). In multivariable analysis, patients with anti-Scl-70 autoantibodies and patients with anti-RNAP-III autoantibodies had an increased risk for conduction blocks, although for the latter, this was not statistically significant (Table 5).

Pericardial effusion was one of the less frequent types of heart involvement. This complication evolved more frequently and more rapidly in men, compared to women (incidence ratio 2.7, 95%CI 1.4-5.4) and in patients with diffuse compared to limited skin involvement (incidence ratio 5.6, 95%CI 2.3-16.5). There was no evidence for a difference between age strata. It is noteworthy, that none of the patients with ACA developed a pericardial effusion, compared to

26% (95%CI 17-39) of patients with anti-Scl-70 autoantibodies. In multivariable analysis, neither patient's sex nor the extent of skin involvement were confirmed as significant risk factors (**Table 5**).

During the first 3 years after RP onset, a LVEF<50% was only observed in 5% of patients (95%CI 3-9; **Figure 14**).

Figure 14. Kaplan-Meier curves of incident cardiac manifestations after RP onset in SSc in the study population.
Hash marks represent censored observations.



Gastrointestinal symptoms

GI symptoms was one of the most common disease features; at baseline 57% of patients reported oesophageal symptoms, 19% stomach symptoms and 17% intestinal symptoms. There was no evidence for a difference in the cumulative percentages of GI symptoms when stratifying by sex, or autoantibody status (p=0.66 and p=0.16, respectively). However, older

patients and patients with diffuse skin involvement tended to acquire a GI symptoms earlier and more frequently (p=0.02 and p=0.02, respectively). In multivariable analysis, older age was a borderline risk factor (HR 1.01 per 1 year increase in age, 95%CI 1.00-1.02) in contrast to diffuse skin involvement (diffuse *vs.* limited: HR 1.35, 95%CI 1.04-1.76); in addition, patients with anti-RNAP-III were less likely to develop GI symptoms than patients with ACA or anti-Scl-70 autoantibodies (HR 0.55, 95%CI 0.34-0.90; HR 0.59, 95%CI 0.39-0.91, respectively).

Urogenital involvement

Around 3% (95%CI 2-5) of patients developed a renal crisis within 1 year after the onset of RP (Figure 12). The majority of patients who developed a renal crisis did so within the first 4 years. Men had a 2.5 times (95%CI 1.2-5.2) higher incidence than women (Figure 13M). There was no difference between younger and older patients (Figure 13N). The cumulative percentage of renal crisis varied markedly between the autoantibody groups (Figure 13O). Patients with anti-RNAP-III autoantibodies had a 4.6 times (95%CI 1.6-12.4) higher incidence of renal crisis than patients harbouring anti-Scl-70 and none of the patients with ACA developed a renal crisis. Patients with diffuse skin involvement developed a renal crisis earlier and more frequently than patients with a limited skin involvement (Figure 13P). In multivariable analysis male sex, anti-RNAP-III positivity, and older age conferred independent risk factors for renal crisis (Table 5).

The IIEF-5 questionnaire was not included in the EUSTAR database at its inauguration. As a consequence, data on erectile dysfunction was only available for 17% (n=32) of men in the study population. Around 52% (95%CI 36-70) of these patients reported an erectile dysfunction (IIEF-5 score<22) during the first 3 years after RP onset progressing to 95% (95%CI 79-100) during the subsequent 6 years. In the first 3 years after onset of RP, about 30% (95%CI 18-52) of the men had developed a severe erectile dysfunction (IIEF-5 score<8). Owing to the small number of men with data on erectile dysfunction, no further stratification was feasible.

DISCUSSION

This longitudinal study uniquely analysed the incidence of organ manifestations in a large cohort of SSc patients early after RP onset and details differences in the evolution of organ involvement. Whereas other investigators have analysed the risk factors for disease manifestation in patients at risk for SSc ("pre-SSc", "very early SSc"), the present study has focused on the analysis of incident organ manifestations in established disease [Minier *et al.*, 2014; Valentini, 2015].

Skin sclerosis, symptoms of GI tract and a reduced pulmonary diffusing capacity were frequent complications of early SSc, incident cardiac complications and pulmonary restriction were observed more rarely, followed by elevated systolic pressures of the pulmonary artery and renal crisis. Our study also highlights a high incidence of diastolic dysfunction, whereas other cardiac complications (conduction blocks, pericardial effusion and left ventricular systolic dysfunction) were less frequent [Komócsi *et al.*, 2012].

In every organ system analysed, approximately half of all organ manifestations that occurred during the 10 year observation period became evident within the first 2 years after RP onset. Thus, the disease onset followed a simultaneous rather than sequential manifestation pattern. Regardless of the differences in the observed frequencies, i.e. the height of the cumulative incidences, of these manifestations, the steep increase in manifestations during the first two years after RP onset were persistently observed across all organs manifestations studied; even complications which are regarded as more severe were not restricted to later disease. Another important point is that approximatively 75% of the patients develop organ involvement during the 5 first years of the disease. This is good news for the patients who reach that point without any organ involvement.

In line with retrospective prevalence estimates, there were differences in the risk factors governing the onset of organ complications [Kuwana *et al.*, 1993; Walker *et al.*, 2007; Hachulla *et al.*, 2009; Assassi *et al.*, 2010; Nguyen *et al.*, 2011; Nikpour *et al.*, 2011; Nihtyanova *et al.*, 2014]. These risk factors modified the cumulative incidences of the organ manifestations but did not substantially modify the steep increase in manifestation rates during the first 2 years after RP onset. This observation, together with the short interval between RP onset and the first non-RP manifestation demonstrates rapid initial disease kinetics and suggests a relatively

short 'window of opportunity' to prevent incident organ damage [Matucci-Cerinic *et al.*, 2013]. Other investigations have also suggested that a variety of severe organ complications (pulmonary hypertension and lung fibrosis, among others) are not restricted to late disease [Steen *et al.*, 2000; Hachulla *et al.*, 2009].

The large number of SSc patients and the longitudinal and multinational setup of this study are strengths of this investigation. Our study also uniquely simulated an inception cohort by including only patients into the *study population* who had a baseline visit within the first year after RP onset. At the same time we introduced a selection bias, as evidenced by the high prevalence of factors commonly associated with more prevalent and severe organ complications (male sex, older age at SSc onset and anti-Scl-70 autoantibodies) [Perera *et al.*, 2007; Walker *et al.*, 2007; Graf *et al.*, 2012; Nihtyanova *et al.*, 2014; Elhai *et al.*, 2016]. This patient selection could account for the previously unreported association of male sex and renal crisis identified in this study and underlines that our findings are specific to SSc patients who present with SSc early after RP onset and must not be generalized to all individuals who present with SSc. However, as also demonstrated in this study, more than half of all patients in the *entire EUSTAR cohort* experienced their first non-RP feature of the disease within one year of the onset of RP. It must be also noted, that some SSc patients had documented organ manifestations already at their baseline visit, leading to an overestimation of the time to its onset. Lastly, our data may be biased by centre specific differences in the assessment of some organ manifestations. With regard to diastolic dysfunction for example, different diagnostic approaches are available, each differing in sensitivity and specificity and predictive value [Faludi *et al.*, 2014]. Also, the in the EUSTAR database the DLCO collected is not corrected for haemoglobin.

Despite these limitations, our data will likely improve the counselling and management of SSc patients early after RP onset. Our findings also have implications for the design of new diagnostic strategies and therapeutics aimed to 'widen' the still very narrow 'window of opportunity' [Matucci-Cerinic *et al.*, 2013].

5. SMOKING, A MODIFIABLE RISK FACTOR – DOES IT MAKE IT WORSE?

ARTICLE 3: SMOKING IN SYSTEMIC SCLEROSIS: A LONGITUDINAL EUROPEAN SCLERODERMA TRIALS AND RESEARCH GROUP STUDY.

Veronika K. Jaeger[1], Gabriele Valentini[2], Eric Hachulla[3], Franco Cozzi[4], Oliver Distler[5], Paolo Airó[6], Laszlo Czirják[7], Yannick Allanore[8], Elise Siegert[9], Edoardo Rosato[10], Marco Matucci-Cerinic[11], Cristian Caimmi[12], Jörg Henes[13], Patricia E. Carreira[14], Vanessa Smith[15,16], Francesco del Galdo[17], Christopher P. Denton[18], Susanne Ullman[19], Ellen De Langhe[20], Valeria Riccieri[21], Juan J. Alegre-Sancho[22], Simona Rednic[23], Ulf Müller-Ladner[24], Ulrich A. Walker[1], EUSTAR co-authors

[1] Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[2] Rheumatology Department, Second University of Naples, Naples, Italy
[3] Service de Médecine Interne, Hôpital Huriez, Université de Lille, Lille, France
[4] Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy
[5] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[6] UO Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italy
[7] Department of Rheumatology and Immunology, University of Pécs, Pécs, Hungary
[8] Department of Rheumatology A, Paris Descartes University, Cochin Hospital, France, Paris
[9] Department of Rheumatology and Immunology, University Hospital Charité, Berlin, Germany
[10] Department of Clinical Medicine, Clinical Immunology Unit-Scleroderma Center, Sapienza University of Rome, Rome, Italy
[11] Department of Experimental and Clinical Medicine, University of Florence & Divison of Rheumatology AOUC, Florence Italy
[12] Unit of Rheumatology, University of Verona, Verona, Italy
[13] Department of Internal Medicine II, Eberhard-Karls-University Tübingen, Tübingen, Germany.
[14] Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain
[15] Faculty of Internal Medicine, Ghent University, Ghent, Belgium,
[16] Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
[17] Leeds Musculoskeletal Biomedical Research Unit (LMBRU), University of Leeds, Leeds, United Kingdom
[18] Department of Rheumatology, University College London, Royal Free Hospital, London, United Kingdom
[19] Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Denmark
[20] Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium,
[21] Rheumatology Unit, Department Of Internal Medicine and Medical Specialities, Sapienza University of Rome, Italy
[22] Sección de Reumatología, Hospital Universitario Dr Peset, Valencia, Spain,

[23] Clinica Reumatologie, University of Medicine & Pharmacy, Cluj-Napoca, Romania
[24] Department of Rheumatology and Clinical Immunology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany

EUSTAR CO-AUTHORS:

Lidia P. Ananieva, Florenzo Iannone, Jörg H.W. Distler, Eduardo Kerzberg, Bojana Stamenkovic, José Antonio Pereira Da Silva, Ivan Catellví, Sule Yavuz, Kamal Solanki, Branimir Anic, Esthela Loyo, Tim Schmeiser, Ruxandra Maria Ionescu, Peter Villiger, Francesco Paolo Cantatore, Paloma García de la Peña Lefebvre, Carina Mihai, Dominique Farge Bancel, Pierluigi Meroni, Thierry Martin, Stefan Heitmann, Nicolas Hunzelmann, Fahrettin Oksel, Washington Bianchi, Sara Bongiovanni, Radim Becvar, Thierry Zenone, Alexandra Balbir-Gurman, Piotr Wiland, Pawel Zebryk, François Spertini, Lori Chung, Alessandra Vacca, Carlo Chizzolini, Carlo Francesco Selmi, Cristina-Mihaela Tanaseanu, Ira Litinsky, Frédéric A. Houssiau, Brigitte Krummel-Lorenz, Vivien M. Hsu, Francisca Fontes, Alexandra Maria Burlui, Duska Martinovic, Sergei Popa, Itzhak Rosner, Carmel Mallia, Rosario Foti, Luc Mouthon, Martin Aringer, Jacob van Laar, Roger Hesselstrand, Maria Rosa Pozzi, Gabriela Riemekasten, Maurizio Cutolo, Paul Hasler, Zea Mendoza Antonio, Cord Sunderkötter, Codrina Ancuta, Jean Sibilia, Roberto Caporali, Armando Gabrielli, Raffaele Pellerito, Ariane Herrick, Øyvind Midtvedt, Kilian Eyerich, Brigitte Granel, Lesley Ann Saketkoo, Maura Couto, Yael Eizikovits, Giuseppina Abignano.

CORRESPONDING AUTHOR: Ulrich A. Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland; Phone: +41 61 5565011; Fax: +41 61 26 59021; E-mail: ulrich.walker@usb.ch

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DATA SHARING: Data is available from the EUSTAR group upon valid scientific request.

CONTRIBUTORSHIP: VKJ and UAW designed the study, analysed and interpreted the data and wrote the manuscript, OD and YA advised in the study design. All authors were involved in data acquisition, and drafting of the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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ABSTRACT

Objectives

Data on the role of tobacco exposure in SSc severity and progression are scarce. We aimed to assess the effects of smoking on the evolution of pulmonary and skin manifestations in the EUSTAR database.

Methods

Adult SSc patients with data on smoking history and a 12-24 months follow-up visit were included. Associations of severity and progression of organ involvement with smoking history and the CSI were assessed using multivariable regression analyses.

Results

3,319 patients were included (age 57 years; 85% female), 66% were never smokers; 23% ex-smokers and 11% were current smokers. Current smokers had a lower percentage of anti-Scl-70 autoantibodies than previous or never smokers (31% vs. 40% and 45%, respectively).

Never smokers had a higher baseline FEV1/FVC ratio than previous and current smokers ($p<0.001$). The FEV1/FVC ratio declined faster in current smokers than in never smokers ($p=0.05$) or ex-smokers ($p=0.01$).

The baseline mRSS and the mRSS decline were comparable across smoking groups. Although heavy smoking (more than 25 pack years) increased the odds of digital ulcers by almost 50%, there was no robust adverse association of smoking with DU development.

Conclusion

The known adverse effect of smoking on bronchial airways and alveoli is also observed in SSc patients; however, robust adverse effects of smoking on the progression of SSc-specific pulmonary or cutaneous manifestations were not observed.

INTRODUCTION

SSc is a rare, multisystem autoimmune disorder [Gabrielli *et al.*, 2009]. Hypoxia and oxidative stress have been implicated in the pathophysiology of its generalized microangiopathy and fibrosis [Gabrielli *et al.*, 2009]. Although smoking does not appear to confer a risk for SSc development [Chaudhary *et al.*, 2011], it has vasoconstrictive effects and increases free radical exposure, and together with other proinflammatory and immunomodulatory effects may exacerbate SSc manifestations [Zhang *et al.*, 2017]. Data on the role of tobacco exposure with regards to the severity of SSc organ manifestations and progression are however scarce and at times contradictory [Hudson *et al.*, 2011]. A Canadian cohort study of 606 patients for example reported an increased frequency of DU in smokers [Hudson *et al.*, 2011], whereas a study of 172 Australian patients, found no association of smoking history with vascular characteristics [Hissaria, Roberts-Thomson, *et al.*, 2011].

Larger studies and robust data assessing the possible effect of smoking on SSc presentations and importantly SSc progression are lacking. We therefore assessed the association of tobacco exposure with the prevalence and evolution of SSc organ manifestations.

METHODS

This study is based on the multinational, longitudinal EUSTAR database [Walker *et al.*, 2007]. Each centre obtained local ethical committee approval; each patient provided written informed consent. Data collection started in 2004. The smoking module, however, was introduced to the database in 2013; hence, smoking data were only collected from that date onwards. Data for this study were exported in May 2017.

Patients were included if they were older than 18 years, fulfilled the 1980 ACR or 2013 ACR/EULAR criteria for SSc, and if the smoking status was known; additionally, patients were required to have a follow-up visit 12-24 months after baseline. Information about the core data collected in EUSTAR can be found elsewhere [Walker *et al.*, 2007]. The EUSTAR smoking module

collects patient-reported smoking status (never/previous/current smoker), the number of pack-years, and the smoking start and cessation dates.

The influence of smoking behaviour was assessed on several disease parameters: FEV1/FVC ratio, FVC, DLCO/sb, PAPsys, mRSS and DU. Further information about outcome measures as well as variables describing the study population can be found in Supplementary Table 2.

Outcome progression was downscaled to 'rate of change per 12 months' unless otherwise stated.

Statistical analysis

Frequencies/percentages or means/SD were calculated; groups were compared using X^2-tests/Fisher's exact tests or t-tests/ANOVA. Multiple linear and logistic regression analyses were applied to adjust outcome/exposure associations with *a priori* defined potential confounding factors (age, sex, time since the onset of RP and since the first non-RP manifestation, antibody status, and skin involvement). As the SSc specific antibodies might be on the causal pathway between smoking and SSc organ involvement we additionally analysed the data without adjustment for antibody status, these results can be found in the supplementary (Supplementary Table 3, Supplementary Table 4, Supplementary Table 5).

Three smoking metrics were modelled separately: (Model 1) never/previous/current smoking, (Model 2) smoking intensity (pack-years; never smokers = 0 pack-years, light smokers = 0-10 pack-years, medium smokers = 10-25 pack-years, heavy smokers = >25 pack-years), and (Model 3) CSI. The CSI is an index incorporating smoking duration, time since cessation and smoking intensity into a single variable [Dietrich *et al.*, 2004; Leffondré *et al.*, 2006]. The CSI depends on two parameters which are estimated for each outcome separately: the half-life, i.e. the rate at which the smoking's impact decays over time, and the lag-time, i.e. the delay between smoking and its impact.

Never smokers carry a CSI of 0 and higher CSI values indicate more smoking. The CSI values are estimated separately for each outcome variable and hence the CSIs including their ranges are different for each outcome variable. The results from the CSI regression analyses should be interpreted in the following way: The beta values represent the additive increase or decrease

in the outcome variable per unit increase in the CSI. The OR values represent the increase in odds for the presence of the outcome variable per unit CSI increase. OR values larger than one indicate that increased smoking increases the likelihood of occurrence of the outcome.

Missing data were imputed using multiple imputation with chained equations [Little, 1988]. The regression analyses shown in this paper are all based on imputed data; the results based on a complete case analysis are represented in Supplementary Table 7. Analyses were performed with Stata/IC 15.1 (StataCorp, USA).

RESULTS

Patient and smoking characteristics

Of the 12,912 adult SSc patients within EUSTAR, 6179 (48%) patients had no smoking data available; in 3414 (26%) patients had no follow-up visit in the required time frame. Therefore, 3,319 (26%) patients fulfilled the inclusion criteria (Supplementary Figure 2). The included patients had clinically similar demographic and disease characteristics than the excluded patients (Supplementary Table 6). On average, a follow-up visit was recorded 1.4 years (SD 0.33) after baseline. Patients were on average 57 years old and 85% were female. Demographic and disease characteristics are shown in Table 6.

66% of patients were never smokers, 23% ex-smokers and 11% were current smokers; 13% of the current smokers (1.5% of patients) stopped smoking during the observation time on average 9 months after the baseline visit. The average ex-smokers had smoked 18 pack-years (SD 21) during a time of 19 years (SD 12) and ceased smoking 15 years (SD 13) ago. 49% of the ex-smokers had ceased smoking before RP onset and 58% had quit before the onset of the first non-RP manifestation. The average current smoker had smoked 27 pack-years (SD 30) during a time of 30 years (SD 13).

Table 6. Baseline demographic and disease characteristics as well as outcome measures by smoking status.
*based on the follow-up visit, not the 12 months projection. **The changes in outcomes are given downscaled to "per 12 month". #Number of patients with available information for each variable.

Characteristics of the study population		n#	Never smokers % or mean (SD)	Ex-smokers % or mean (SD)	Current smokers % or mean (SD)	p-value
N			2205	752	362	
Age; years		3319	57.5 (14.1)	57.2 (12.1)	52.5 (11.2)	<0.001
Male sex		3319	8	27	29	<0.001
Disease characteristics						
Time since RP onset; years		3286	14.9 (11.7)	13.4 (11.3)	13.3 (11.8)	0.001
Time since first non-RP manifestation; years		2988	11.7 (8.8)	10.5 (8.7)	8.9 (7.8)	<0.001
Skin involvement	Sine	3106	7	8	15	<0.001
	Limited		64	62	58	
	Diffuse		29	30	27	
mRSS		2949	7.7 (7.4)	7.8 (7.9)	6.9 (7.3)	0.14
Follow-up mRSS*		2839	7.4 (7.2)	7.2 (7.1)	6.9 (6.9)	0.40
Change in mRSS**		2684	-0.3 (3.4)	-0.6 (4.0)	-0.2 (3.3)	0.12
Oesophageal symptoms		3275	60	66	58	0.010
Stomach symptoms		3241	23	23	21	0.68
Intestinal symptoms		3250	27	30	29	0.24
Dyspnoea; NYHA functional class	I	3114	57	54	63	0.001
	II		33	34	31	
	III		9	10	5	
	IV		1	2	1	
Digital ulcers, current		3125	14	14	16	0.7
Digital ulcers, ever		3125	46	48	45	0.56
LVEF; %		2448	62.3 (6.1)	61.7 (6.3)	63.0 (5.8)	0.015
FEV1/FVC ratio		2256	97.5 (13.5)	95.4 (15.2)	92.8 (15.0)	<0.001
Follow-up FEV1/FVC ratio*		1988	97.1 (12.0)	95.4 (14.5)	90.5 (12.7)	<0.001
Change in FEV1/FVC ratio**		1656	-0.3 (10.1)	0.4 (9.4)	-1.6 (7.7)	0.065
FVC; % of predicted		2720	96.1 (22.0)	96.7 (21.3)	98.3 (19.7)	0.25
Follow-up FVC*; % of predicted		2435	95.5 (22.8)	96.3 (22.5)	99.3 (18.8)	0.037
Change in FVC**; % of predicted		2166	-0.6 (8.5)	-0.4 (7.7)	0.1 (9.4)	0.45
DLCO/sb; % of predicted		2583	69.8 (19.6)	66.4 (20.4)	67.1 (17.8)	<0.001
Follow-up DLCO/sb*; % of predicted		2253	67.5 (20.0)	65.6 (20.0)	64.4 (18.1)	0.021
Change in DLCO/sb**; % of predicted		1977	-2.0 (9.1)	-1.7 (9.2)	-2.0 (7.8)	0.86
PAPsys; mmHg		2317	28.8 (16.9)	26.0 (1.0)	24.3 (12.5)	<0.001

Characteristics of the study population	n#	Never smokers % or mean (SD)	Ex-smokers % or mean (SD)	Current smokers % or mean (SD)	p-value
Follow-up PAPsys*; mmHg	2055	29.2 (13.6)	28.5 (14.1)	24.7 (11.6)	<0.001
Change in PAPsys**; mmHg	1706	0.6 (10.5)	1.6 (8.5)	0.2 (8.1)	0.18
Laboratory parameters					
ACA positive	2508	47	47	61	
Anti-Scl-70 positive		45	40	31	<0.001
Anti-RNAP-III positive		3	6	6	
ESR; mm/hr	2795	22.8 (18.4)	18.9 (16.7)	18.0 (14.5)	<0.001

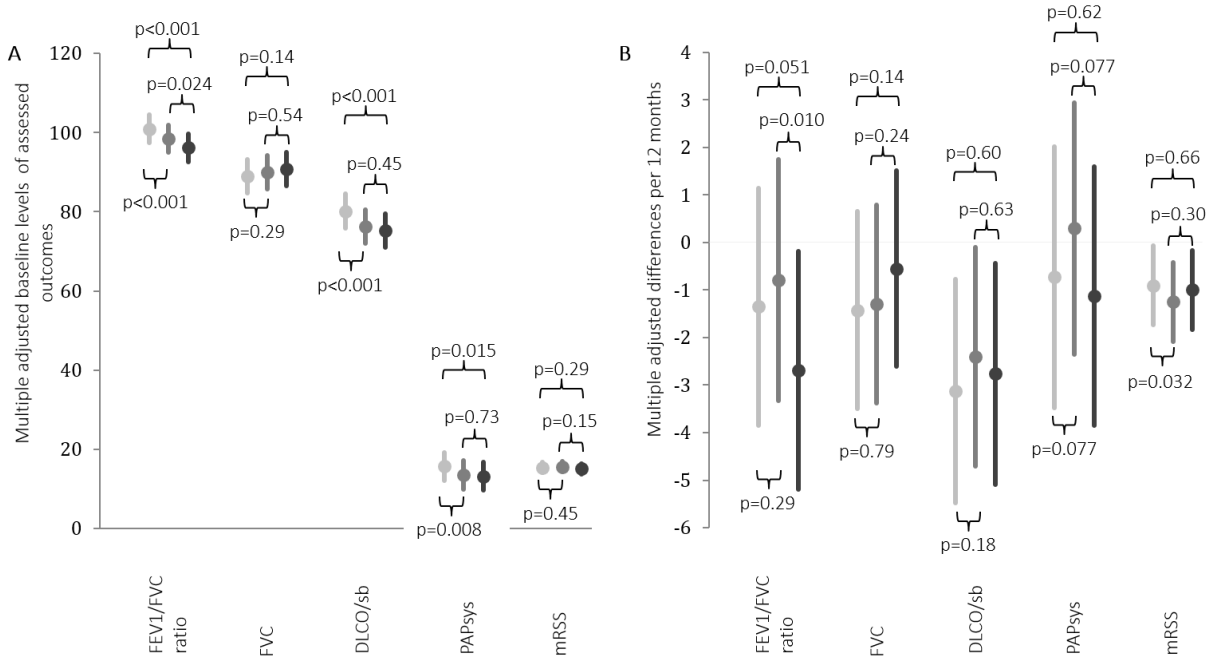
As patients with ILD might be more likely to cease smoking than patients without ILD there might be a higher percentage of ILD patients in the previous smoker group possibly leading to worse trajectories in lung function measures. Therefore, in addition to analysing the entire study population, we also analysed the progression of lung function measures separately for patients with ILD on HRCT and patients without ILD on HRCT. Among all patients, 49% had signs of ILD on HRCT. The smoking behaviour patterns were similar in patients with ILD and in patients without ILD; 68% of patients in both groups were never smokers, 23% of patients with and 20% of patients without ILD were previous smokers, and 9% of patients with and 12% of patients without ILD were current smokers (p=0.06).

FEV1/FVC ratio

Never smokers had a significantly higher baseline FEV1/FVC ratio than previous and current smokers (**Table 6**). These differences in baseline FEV1/FVC ratio were seen in all three smoking models (**Figure 15**; **Table 7**; **Supplementary Table 8**). As can be seen in **Table 7**, patients had a 2.7 unit lower FEV1/FVC ratio per unit increase in the CSI. Medium and heavy smokers had lower baseline FEV1/FVC ratios than never smokers and light smokers (all p<0.001; **Supplementary Table 8**). In univariable analysis, the FEV1/FVC ratio declined similarly across smoking groups (p=0.065); in multivariable analysis, the FEV1/FVC ratio however declined

faster in current smokers (**Figure 15**); this result was also observed when stratifying the study population into ILD and non-ILD patients (data not shown).

Figure 15. Regression analysis comparing outcomes by smoking status adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.
Panel A shows the multiple adjusted baseline levels of the outcome measures and corresponding 95% confidence intervals and panel B shows the multiple adjusted change rates in the outcome measures between baseline and the projected 12 months follow-up. Light grey represents never smokers, medium grey represents ex-smokers and dark grey represents current smokers.



FVC

There was no significant difference in baseline FVC and in the FVC change between the three smoking groups (**Table 6**). This lack of a robust effect of smoking on the baseline FVC and on the FVC change was also observed in all three multivariable models (**Figure 15**; **Table 7**;

Supplementary Table 8). This lack was also observed when assessing the FVC changes separately for ILD and non-ILD patients (data not shown).

Table 7. Regression analysis comparing outcomes at baseline and progression of outcomes according to the comprehensive smoking index (CSI) adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.
The first column illustrates the mean and the range of each outcome's CSI based on the imputed dataset. Higher CSIs indicate more smoking; never smokers carry a CSI of 0.
The beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI. The OR values represent the increase in odds for the presence of the outcome variable per unit CSI increase. OR values larger than one indicate that increased smoking increased the likelihood of occurrence of the outcome.
The follow-up part of the table assesses the projected change per 12 months of the outcomes.

Outcomes	Mean CSI (range)	CSI β or OR	CSI 95%CI	p-value
Baseline				
FEV1/FVC	0.45 (0-4.09)	β= -2.71	-3.46 to -1.97	<0.001
FVC	0.34 (0-5.12)	β= 0.41	-0.39 to 1.22	0.32
DLCO/sb	0.27 (0-2.94)	β= -4.38	-5.89 to -2.88	<0.001
PAPsys	0.23 (0-2.61)	β= -2.08	-3.57 to -0.58	0.006
mRSS	0.40 (0-7.05)	β= 0.20	-0.03 to 0.43	0.088
DU current	0.35 (0-7.94)	OR= 1.19	1.07 to 1.32	0.002
Follow-up				
FEV1/FVC	0.33 (0-6.69)	β= -0.45	-0.93 to 0.02	0.059
FVC	0.46 (0-6.36)	β= 0.32	-0.01 to 0.66	0.059
DLCO/SB	0.43 (0-4.02)	β= 0.37	-0.16 to 0.90	0.17
PAPsys	0.35 (0-6.19)	β= -0.21	-0.76 to 0.34	0.45
mRSS	0.43 (0-6.36)	β= -0.16	-0.29 to -0.02	0.021
DU new btw visits	0.30 (0-8.37)	OR= 0.83	0.68 to 1.00	0.056

DLCO/sb

Smokers had lower baseline DLCO/sb levels than never smokers (p<0.001; **Table 6**); smoking was associated with low baseline DLCO/sb in all three models (**Figure 15**; **Table 7**; **Supplementary Table 8**). The DLCO/sb declined similarly across all three smoking behaviour

groups in univariable (Table 6) and multivariable analysis (Figure 15; Table 7; Supplementary Table 8), these results were also true when looking at ILD and non-ILD patients separately (data not shown).

PAPsys

The average baseline PAPsys was slightly higher in never smokers than in current or ex-smokers (Table 6). These differences stayed apparent but to a lesser extent not only when assessing the smoking groups multivariably, but also evaluating smoking intensity and the CSI (Figure 15; Table 7; Supplementary Table 8). The PAPsys increased similarly in the groups in univariable (Table 6) and multivariable analysis (Figure 15; Table 7; Supplementary Table 8).

Skin involvement

No association was evident between the severity of skin fibrosis and the smoking history regardless of the smoking matrices used (Table 6; Figure 15; Table 7; Supplementary Table 8). SSc sine scleroderma, however, was twice as prevalent in current as in ex- or never smokers (Table 6). In all smoking models, no clinically significant difference in mRSS evolution was observed (Table 6; Figure 15; Table 7; Supplementary Table 8).

DU

The prevalence of DUs was comparable in the smoking behaviour groups (Table 6). However, heavy smokers had a greater likelihood of DUs than never smokers in multivariable analysis (OR=1.6, p=0.02; Supplementary Table 8); also, a higher CSI was associated with the presence of DUs at baseline (OR=1.2, p=0.002, i.e. for a one unit increase in CSI, the odds of having DUs at baseline increases by a factor of 1.19; Table 7).

In the sub-group of DU-naïve patients at baseline, 14% of never smokers developed new DUs in between the two visits, compared to 16% ex-smokers and 8% current smokers (p=0.05). Ex-smokers had comparable odds than never smokers to develop DU between the two visits

(OR=1.1, p=0.7); current smokers developed DUs less often than never smoking patients (OR=0.5, p=0.031). The smoking intensity was not associated with incident DU during the observation period (Supplementary Table 8).

DISCUSSION

Our study is by far the largest prospectively investigating the effect of smoking on SSc outcomes. Smoking was common in our patients, however less than in Anglo-Saxon cohorts and also much lower than the European average of around 28% [Hissaria, Roberts-Thomson, *et al.*, 2011; Hudson *et al.*, 2011; World Health Organization, 2017].

The EUSTAR cohort replicated the known adverse effect of smoking on bronchial airways in terms of a decline in FEV1/FVC and DLCO. Given the absence of discernible adverse effects of smoking on PAPsys the effect of smoking on diffusion capacity may reflect emphysema rather than precapillary pulmonary vasculopathy. Adverse effects of smoking on pulmonary airway obstruction and diffusing capacity were also seen in two cohorts of 137 SSc and 19 smokers [Steen *et al.*, 1985; Greenwald *et al.*, 1987]. In line with one of these cohorts [Steen *et al.*, 1985] but in contrast to the second study [Greenwald *et al.*, 1987] we found no association between lung compliance (FVC) and smoking status.

Our study also found no robust effect of smoking on DU prevalence and incidence when assessing the smoking behaviour itself or assessing the smoking intensity, similar to two smaller studies [Alivernini *et al.*, 2009; Khimdas *et al.*, 2011]. We even found a negative association between tobacco exposure and incident DU during the follow-up in a sub-group of DU naïve patients (OR=0.5). This effect could not be explained by differences in immunosuppressive and vasoactive medication (data not shown). However, when we assessed smoking using the CSI we did find an association of smoking on DU prevalence similar to another, however quite smaller study also using the CSI [Hudson *et al.*, 2011]. This difference could partially arise due to a 'healthy smoker effect', although this bias is partly been accounted for by the CSI [Becklake *et al.*, 1990]. Given these results, it is difficult to draw robust conclusions on the effect of smoking on DUs.

In our study, smokers had a lower prevalence of anti-Scl-70 autoantibodies than previous and never smokers. This imbalance in autoantibody status is also in line with that found in another study, in which anti-Scl-70 positive patients were more likely to be never smokers than ever smokers [Chaudhary *et al.*, 2011] raising the possibility of a aethiopathological link between smoking and anti-Scl-70 positivity. The question, however, is if this imbalance is partly due to a link, maybe a causal one, between smoking and autoantibody status or if this imbalance is partly explained by a 'healthy smoker effect' especially as the prevalence of anti-Scl-70 positivity in previous smokers is more comparable to the never smokers than to current smokers.

Like all registry-based studies the EUSTAR cohort has limitations. We had no means to verify the smoking information provided by the patients; however, we were able to demonstrate known adverse effects of smoking on airway obstruction suggesting that the information provided by the patients was not random and that our study was powered to detect meaningful changes in other parameters.

By requiring the study population to have a follow-up visit there is a possibility that we excluded sicker patients, i.e. that we introduced a selection bias for healthier patients. However, at baseline the patients that were excluded due to the absence of a follow-up visit within the required time frame were not majorly worse off than the included patients (Supplementary Table 6) arguing against a major selection bias.

In summary, our study demonstrates an adverse effect of smoking on pulmonary airways, but no effects on SSc-specific pulmonary and cutaneous involvement. These data argue against a major role of tobacco associated free radicals, vasoconstrictory and immunomodulatory effects in the pathogenesis of SSc vasculopathy and fibrosis.

SUPPLEMENTARY MATERIAL

Supplementary Table 2. Description of variables selected a priori for the analysis.

Demographics
Age (years)
Sex (female/male)
Disease characteristics
Time since RP onset (years)
Time since first non-RP manifestation (years)
Modified Rodnan skin score (mRSS; range 0 to 51)
Oesophageal symptoms (yes/no; dysphagia, reflux according to patient)
Stomach symptoms (yes/no; early satiety, vomiting according to patient)
Intestinal symptoms (yes/no; diarrhoea, bloating, constipation according to patient)
Dyspnoea (modified NYHA functional class I to IV;
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea (shortness of breath).
Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in dyspnoea.
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes dyspnoea.
Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest.)
Digital ulcers (yes/no; current ulcers distal to or at the proximal interphalangeal joint)
Systolic pulmonary artery pressure (PAPsys, mmHg; as estimated by echocardiography)
Single breath diffusing capacity for carbon monoxide (DLCO, % of predicted)
Forced vital capacity (FVC, % of predicted)
Forced expiratory volume in one second; (FEV1, % of predicted)
Left ventricular ejection fraction (LVEF, %)
Laboratory
Anticentromere autoantibodies positivity (ACA; yes/no)
Anti-topoisomerase autoantibodies positivity (anti-Scl-70; yes/no)
Anti-RNA polymerase-III autoantibodies positivity (anti-RNAP-III; yes/no)
Erythrocyte sedimentation rate (ESR; mm/hour)

Supplementary Table 3. Linear and logistic regression analyses comparing outcomes in previous and current smokers with that of never smokers adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, and extent of skin involvement but not adjusted for antibody status.
Results are based on the multiple imputed data.
The beta values represent the increase or decrease in the outcome variable of previous or current smokers compared to never smokers. The OR values represent the increase in odds for the presence of the outcome variable of previous or current smokers compared to never smokers. The follow-up part of the table assesses the projected change per 12 months of the outcomes.

Outcomes	Previous smokers			Current smokers		
	β or OR	95%CI	p-value	β or OR	95%CI	p-value
Baseline						
FEV1/FVC	β= -2.82	-4.2 to -1.4	<0.001	β= -5.72	-7.5 to -3.9	<0.001
FVC (% of predicted)	β= 1.72	-0.1 to 3.5	0.063	β= 4.23	1.8 to 6.6	0.001
DLCO/sb (% of predicted)	β= -3.53	-5.3 to -1.8	<0.001	β= -3.63	-6.0 to -1.3	0.003
PAPsys (mmHg)	β= -2.11	-3.6 to -0.6	0.006	β= -2.76	-4.7 to -0.8	0.006
mRSS	β= 0.14	-0.4 to 0.6	0.60	β= -0.42	-1.1 to 0.3	0.23
DU current	OR= 1.02	0.8 to 1.3	0.89	OR= 1.19	0.9 to 1.6	0.31
Follow-up						
FEV1/FVC	β= 0.64	-0.4 to 1.7	0.22	β= -1.18	-2.5 to 0.2	0.085
FVC (% of predicted)	β= 0.11	-0.8 to 1.0	0.80	β= 0.74	-0.4 to 1.9	0.22
DLCO/sb (% of predicted)	β= 0.74	-0.3 to 1.8	0.17	β= 0.25	-1.1 to 1.6	0.73
PAPsys (mmHg)	β= 1.00	-0.1 to 2.1	0.082	β= -0.29	-1.9 to 1.3	0.72
mRSS	β= -0.39	-0.7 to -0.1	0.014	β= -0.14	-0.6 to 0.3	0.51
DU new btw visits	OR= 1.08	0.8 to 1.5	0.66	OR= 0.50	0.3 to 0.9	0.018

Supplementary Table 4. Linear and logistic regression analyses comparing outcomes in light, medium or heavy smokers with that of never smokers adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, and extent of skin involvement but not adjusted for antibody status.
Results are based on the multiple imputed data.
The beta values represent the increase or decrease in the outcome variable of light, medium or heavy smokers compared to never smokers. The OR values represent the increase in odds for the presence of the outcome variable of light, medium or heavy smokers compared to never smokers. The follow-up part of the table assesses the projected change per 12 months of the outcomes.

Outcomes	>0 to 10 pack-years			>10 to 25 pack-years			>25 pack-years		
	β or OR	95%CI	p-value	β or OR	95%CI	p-value	β or OR	95%CI	p-value
Baseline									
FEV1/FVC	β= -1.84	-3.7 to 0.01	0.050	β= -4.41	-6.4 to 2.5	<0.001	β= -6.01	-8.2 to -3.8	<0.001
FVC (% of predicted)	β= 3.28	1.0 to 5.5	0.004	β= 3.19	0.6 to 5.8	0.016	β= 0.48	-2.2 to 3.1	0.73
DLCO/sb (% of predicted)	β= -2.22	-4.4 to -0.1	0.043	β= -2.94	-5.4 to -0.5	0.021	β= -6.43	-9.1 to -3.8	<0.001
PAPsys (mmHg)	β= -1.89	-3.7 to -0.04	0.045	β= -3.01	-5.0 to -1.0	0.003	β= -2.20	-4.4 to 0.02	0.052
mRSS	β= -0.18	-0.8 to 0.5	0.59	β= -0.31	1.0 to 0.4	0.41	β= 0.50	-0.3 to 1.3	0.21
DU current	OR= 0.86	0.6 to 1.2	0.41	OR= 1.07	0.7 to 1.6	0.71	OR= 1.47	1.0 to 2.2	0.045
Follow-up									
FEV1/FVC	β= 0.01	-1.3 to 1.3	0.99	β= -0.24	-1.6 to 1.1	0.72	β= 0.51	-0.9 to 2.0	0.49
FVC (% of predicted)	β= 0.44	-0.7 to 1.5	0.43	β= 0.29	-1.0 to 1.6	0.67	β= 0.14	-1.1 to 1.4	0.83
DLCO/sb (% of predicted)	β= 0.64	-0.6 to 1.9	0.32	β= 0.49	-0.8 to 1.8	0.47	β= 0.59	-0.9 to 2.0	0.42
PAPsys (mmHg)	β= 0.54	-0.8 to 1.9	0.44	β= 0.94	-0.7 to 2.5	0.25	β= 0.28	-1.5 to 2.1	0.76
mRSS	β= -0.37	-0.8 to 0.03	0.067	β= -0.08	-0.52 to 0.37	0.74	β= -0.49	-1.0 to -0.02	0.043
DU new btw visits	OR= 0.80	0.5 to 1.3	0.36	OR= 0.96	0.6 to 1.5	0.88	OR= 0.87	0.5 to 1.5	0.62

Supplementary Table 5. Regression analysis comparing outcomes according to the comprehensive smoking index (CSI) adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, and extent of skin involvement but not adjusted for antibody status.
Results are based on the multiple imputed data.
Higher CSIs indicate more smoking; never-smokers carry a CSI of 0. The beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI. The OR values represent the increase in odds for the presence of the outcome variable per unit CSI increase. OR values larger than one indicate that increased smoking increased the likelihood of occurrence of the outcome.
The follow-up part of the table assesses the projected change per 12 months of the outcomes.

Outcomes	CSI		
	β or OR	95%CI	p-value
Baseline			
FEV1/FVC	β= -3.00	-3.8 to -2.3	<0.001
FVC	β= 1.08	0.3 to 1.9	0.010
DLCO/sb	β= -3.71	-5.2 to -2.2	<0.001
PAPsys	β= -2.26	-3.8 to -0.8	0.003
mRSS	β= 0.19	-0.04 to 0.4	0.11
DU current	OR= 1.16	1.0 to 1.3	0.004
Follow-up			
FEV1/FVC	β= -0.41	-0.9 to 0.1	0.091
FVC	β= 0.28	-0.1 to 0.6	0.099
DLCO/sb	β= 0.33	-0.2 to 0.9	0.22
PAPsys	β= -0.17	-0.7 to 0.4	0.53
mRSS	β= -0.17	-0.3 to -0.04	0.013
DU new btw visits	OR= 0.81	0.7 to 1.0	0.034

Supplementary Table 6. Comparison of included and excluded patients.

Baseline characteristics of the study population		Included patients (mean [SD] or %)	Excluded patients (mean [SD] or %)	p-value (comparing included and excluded patients)	Excluded due to no follow-up visit 12-24 months after baseline (mean [SD] or %)	p-value (comparing included and excluded due to lack of follow-up visit)
N		3319	9593		3414	
Smoking behaviour	Never	66			69	0.001
	Previous	23			19	
	Current	11			12	
Age; years		56.9 (13.5)	55.8 (14.0)	<0.001	55.5	<0.001
Male sex		15	15	0.77	15	0.55
Disease characteristics						
Time since RP onset; years		14.4 (11.6)	12.0 (11.3)	<0.001	11.5 (11.2)	<0.001
Time since first non-RP manifestation; years		11.1 (8.8)	8.5 (9.4)	<0.001	8.1 (9.7)	<0.001
Skin involvement	Sine	8	2	<0.001	6	0.007
	Limited	63	64		64	
	Diffuse	29	34		30	
mRSS		7.7	8.8	<0.001	8.7	<0.001
Oesophageal symptoms		61	64	<0.001	64	0.007
Stomach symptoms		22	23	0.47	21	0.15
Intestinal symptoms		28	24	<0.001	24	0.001
Dyspnoea; NYHA functional class	I	57	54	<0.001	54	0.14
	II	33	34		35	
	III	9	11		10	
	IV	1	1		1	
Digital ulcers, current		14	15	0.40	15	0.41
Digital ulcers, ever		47	43	0.004	43	0.012

LVEF; %	62.2 (6.1)	62.2 (7.0)	0.99	62.3 (6.9)	0.77
FEV1/FVC ratio	96.5 (14.2)	98.6 (14.7)	<0.001	98.0 (14.2)	0.001
FVC; % of predicted	96.5 (21.6)	93.1 (22.0)	<0.001	94.9 (22.5)	0.012
DLCO/sb; % of predicted	68.7 (19.7)	68.8 (28.2)	0.89	70.1 (20.7)	0.015
PAPsys; mmHg	27.7 (16.0)	29.9 (15.6)	<0.001	28.1 (15.2)	0.31
Laboratory parameters					
ACA positive	48	49	<0.001	53	0.002
Anti-Scl-70 positive	43	46		40	
Anti-RNAP-III positive	4	2		3	
ESR; mm/hr	21.4 (17.7)	23.5 (19.9)	<0.001	22.2 (19.4)	0.11

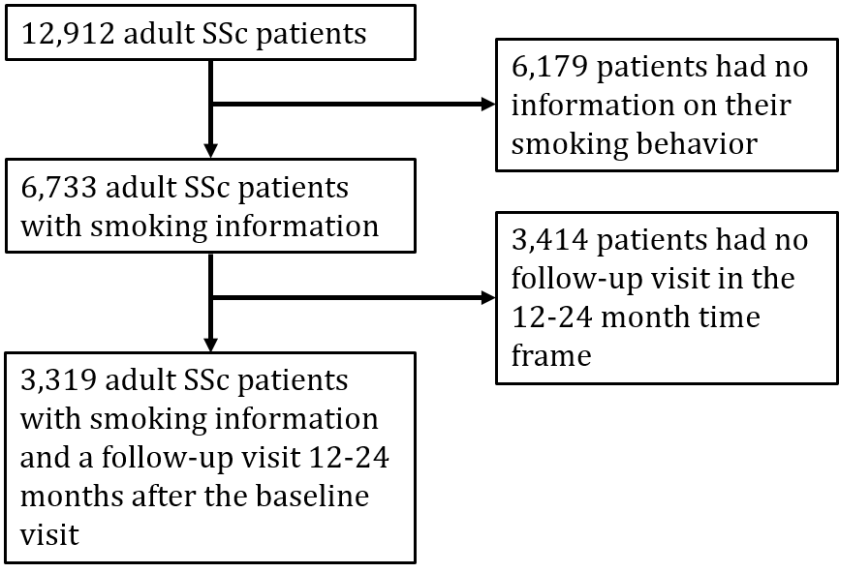
Supplementary Table 7. Linear and logistic regression analyses in previous and current smokers with that of never smokers adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.
Results are based on complete cases.
The beta values represent the increase or decrease in the outcome variable of previous or current smokers compared to never smokers. The OR values represent the increase in odds for the presence of the outcome variable of previous or current smokers compared to never smokers. The follow-up part of the table assesses the projected change per 12 months of the outcomes.

Outcomes	Previous smokers			Current smokers		
	β or OR	95%CI	p-value	β or OR	95%CI	p-value
Baseline						
FEV1/FVC	β= -2.11	-3.9 to -0.3	0.021	β= -5.25	-7.7 to -2.7	<0.001
FVC (% of predicted)	β= 0.43	-1.8 to 2.7	0.70	β= 1.56	-1.5 to 4.6	0.32
DLCO/sb (% of predicted)	β= -3.75	-6.0 to -1.5	0.001	β= -6.02	-9.1 to -2.9	<0.001
PAPsys (mmHg)	β= -2.38	-4.3 to -0.4	0.018	β= -2.17	-4.8 to 0.5	0.11
mRSS	β= 0.03	-0.7 to 0.8	0.94	β= -0.55	-1.6 to 0.5	0.31
DU current	OR= 1.06	0.8 to 1.5	0.71	OR= 1.29	0.9 to 1.9	0.21
Follow-up						
FEV1/FVC	β= 1.02	-0.3 to 2.4	0.14	β= -1.17	-3.0 to 0.7	0.22
FVC (% of predicted)	β= -0.14	-1.2 to 1.0	0.80	β= 1.14	-0.4 to 2.6	0.14
DLCO/sb (% of predicted)	β= 0.31	-1.0 to 1.6	0.63	β= 0.42	-1.3 to 2.1	0.63
PAPsys (mmHg)	β= 0.52	-0.9 to 2.0	0.49	β= -1.19	-3.2 to 0.8	0.24
mRSS	β= -0.43	-0.8 to -0.03	0.033	β= -0.40	-1.0 to 0.1	0.15
DU new btw visits	OR= 1.37	0.9 to 2.1	0.15	OR= 0.65	0.3 to 1.3	0.22

Supplementary Table 8. Linear and logistic regression analysis comparing outcomes in light, medium or heavy smokers with that of never smokers adjusted for age, sex, time since the onset of Raynaud's phenomenon, time since the first non-Raynaud's phenomenon manifestation, antibody status and extent of skin involvement.
The results are based on the multiple imputed data.
The beta values represent the increase or decrease in the outcome variable of light, medium or heavy smokers compared to never smokers. The OR values represent the increase in odds for the presence of the outcome variable of light, medium or heavy smokers compared to never smokers. The follow-up part of the table assesses the projected change per 12 months of the outcome.

Outcomes	>0 to 10 pack-years			>10 to 25 pack-years			>25 pack-years		
	β or OR	95%CI	p-value	β or OR	95%CI	p-value	β or OR	95%CI	p-value
Baseline									
FEV1/FVC	β= -1.50	-3.34 to 0.34	0.11	β= -3.65	-5.59 to -1.72	<0.001	β= -5.35	-7.56 to -3.15	<0.001
FVC (% of predicted)	β= 2.5	0.33 to 4.67	0.024	β= 1.39	-1.12 to 3.91	0.28	β= -1.12	-3.70 to 1.47	0.40
DLCO/sb (% of predicted)	β= -2.57	-4.71 to -0.44	0.018	β= -3.82	-6.33 to -1.31	0.003	β= -7.29	-9.92 to -4.65	<0.001
PAPsys (mmHg)	β= -1.84	-3.69 to 0.01	0.051	β= -2.83	-4.85 to -0.81	0.006	β= -1.97	-4.19 to 0.24	0.080
mRSS	β= -0.13	-0.79 to 0.53	0.71	β= -0.22	-0.94 to 0.51	0.55	β= 0.54	-0.24 to 1.32	0.17
DU current*	OR= 0.89	0.63 to 1.26	0.52	OR= 1.16	0.80 to 1.70	0.43	OR= 1.59	1.08 to 2.34	0.019
Follow-up									
FEV1/FVC	β= -0.018	-1.35 to 1.31	0.98	β= -0.36	-1.72 to 1.00	0.60	β= 0.35	-1.12 to 1.81	0.64
FVC (% of predicted)	β= 0.43	-0.67 to 1.52	0.44	β= 0.34	-0.96 to 1.63	0.61	β= 0.26	-1.02 to 1.54	0.69
DLCO/sb (% of predicted)	β= 0.63	-0.65 to 1.92	0.33	β= 0.53	-0.81 to 1.86	0.44	β= 0.68	-0.75 to 2.11	0.35
PAPsys (mmHg)	β= 0.53	-0.83 to 1.88	0.45	β= 0.92	-0.69 to 2.52	0.26	β= 0.27	-1.56 to 2.10	0.77
mRSS	β= -0.34	-0.74 to 0.06	0.09	β= -0.01	-0.05 to 0.43	0.95	β= -0.44	-0.93 to 0.04	0.07
DU new btw visits*	OR= 0.80	0.49 to 1.30	0.37	OR= 0.99	0.58 to 1.69	0.97	OR= 0.90	0.52 to 1.58	0.72

Supplementary Figure 2. Flow chart of the study population.



6. PHYSICAL FUNCTION IN SYSTEMIC SCLEROSIS - THE PATIENT PERSPECTIVE

ARTICLE 4: FUNCTIONAL DISABILITY AND ITS PREDICTORS IN SYSTEMIC SCLEROSIS: A STUDY FROM THE DESSCIPHER PROJECT WITHIN THE EUSTAR GROUP

Veronika K. Jaeger[1], Oliver Distler[2], Britta Maurer[2], Laszlo Czirják[3], Veronika Lóránd[3], Gabriele Valentini[4], Serena Vettori[4], Francesco Del Galdo[5], Giuseppina Abignano[5], Christopher Denton[6], Svetlana Nihtyanova[6], Yannick Allanore[7], Jerome Avouac[7], Gabriele Riemekasten[8], Elise Siegert[9], Dörte Huscher[10], Marco Matucci-Cerinic[11], Serena Guiducci[11], Marc Frerix[12], Ingo H. Tarner[12], Beata Garay Toth[13], Beat Fankhauser[14], Jörg Umbricht[14], Anastasia Zakharova[15], Carina Mihai[16], Franco Cozzi[17], Sule Yavuz[18], Nicolas Hunzelmann[19], Simona Rednic[20], Alessandra Vacca[21], Tim Schmeiser[22], Valeria Riccieri[23], Paloma García de la Peña Lefebvre[24], Armando Gabrielli[25], Brigitte Krummel-Lorenz[26], Duska Martinovic[27], Codrina Ancuta[28], Vanessa Smith[29], Ulf Müller-Ladner[12], Ulrich A. Walker[1] on behalf of the DeSScipher Consortium and contributing EUSTAR centres

[1] Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[2] Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland
[3] Department of Rheumatology and Immunology, Medical Center, University of Pécs, Pécs, Hungary
[4] Department of Rheumatology, Second University of Naples, Naples, Italy
[5] NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom
[6] Department of Rheumatology, University College London, Royal Free Hospital, London, United Kingdom
[7] Department of Rheumatology, University of Paris Descartes, Paris, France
[8] Department of Rheumatology, University Clinic Schleswig-Holstein, Lübeck, Germany
[9] Department of Rheumatology and Clinical Immunology, University Hospital Charité, Berlin, Germany
[10] German Rheumatism Research Centre, Berlin, Germany
[11] Department of Rheumatology, University of Florence, Florence, Italy
[12] Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerckhoff Clinic Bad Nauheim, Bad Nauheim, Germany
[13] Federation of European Scleroderma Associations aisbl, Budapest, Hungary
[14] new-win SW Solutions AG, Suhr, Switzerland
[15] VA Nasonova Institute of Rheumatology, Moscow, Russian Federation

[16] Department of Internal Medicine and Rheumatology, Dr. Ion Cantacuzino Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[17] Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy
[18] Department of Rheumatology, University of Marmara, Altunizade-Istanbul, Turkey
[19] Department of Dermatology, University of Cologne, Cologne, Germany
[20] Clinica Reumatologie, University of Medicine & Pharmacy, Cluj-Napoca, Romania
[21] II Chair of Rheumatology, University of Cagliari-Policlinico Universitario, Monserrato, Italy
[22] Department of Rheumatology and Immunology, Krankenhaus St. Josef, Wuppertal, Germany
[23] Divisione di Reumatologia, Università di Roma La Sapienza, Roma, Italy
[24] Servicio de Reumatología, Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain
[25] Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica, Università Politecnica delle Marche, Ancona, Italy
[26] Endokrinologikum Frankfurt, Frankfurt, Germany
[27] Division of Rheumatology, University Hospital of Split, Split, Croatia
[28] Rheumatology 2 Department, Clinical Rehabilitation Hospital, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania
[29] Faculty of Internal Medicine, Ghent University, Ghent, Belgium

CORRESPONDING AUTHOR: Ulrich A. Walker, Department of Rheumatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland; Phone: +41 61 32 87479; Fax: +41 61 26 59021; E-mail: ulrich.walker@usb.ch

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ABSTRACT

Objectives

The multisystem manifestations of SSc can greatly impact patients' quality of life. The aim of this study was to identify factors associated with disability in SSc

Methods

SSc patients from the prospective DeSScipher cohort who had completed the SHAQ, a disability score that combines the health assessment questionnaire and five VAS, were included in this analysis. The effect of factors possibly associated with disability was analysed with multiple linear regressions.

Results

The mean SHAQ and HAQ scores of the 944 patients included were 0.87 (SD 0.66) and 0.92 (SD 0.78). 59% of the patients were in the "mild to moderate difficulty" SHAQ category (0≤SHAQ<1), 34% in the "moderate to severe disability" category (1≤SHAQ<2) and 7% in the "severe to very severe disability" category (2≤SHAQ≤3). The means of the VAS scores were in order of magnitude: overall disease severity (37mm), Raynaud's phenomenon (31mm), pulmonary symptoms (24mm), gastrointestinal symptoms (20mm) and digital ulcers (19mm).

In multiple regression, the main factors associated with high SHAQ scores were the presence of dyspnoea (modified NYHA-class IV (regression coefficient B=0.62), modified NYHA III (B=0.53) and modified NYHA II (B=0.21; all vs. modified NYHA-class I), fibromyalgia (B=0.37), muscle weakness (B=0.27), DU (B=0.20) and gastrointestinal symptoms (oesophageal symptoms, B=0.16; stomach symptoms, B=0.15; intestinal symptoms, B=0.15).

Conclusions

SSc patients perceive dyspnoea, pain, DUs, muscle weakness and gastrointestinal symptoms as the main factors driving their level of disability, unlike physicians who emphasize objective measures of disability.

INTRODUCTION

SSc is a rare, clinically heterogeneous multisystem disorder which greatly affects the patients' physical and psychological functioning and impairs their ability to participate in work and social activities. Substantial morbidity results from DU, skeletal muscle weakness, contractures, cardiopulmonary and gastrointestinal involvement [Johnson *et al.*, 2006; Hudson *et al.*, 2009; Mouthon *et al.*, 2010]. One of the most formidable goals of care is to alleviate symptoms and disability and to improve the health-related QoL and functional ability [Kwakkenbos *et al.*, 2013].

Whereas physicians tend to emphasize objective measures of disease status, patients may perceive other aspects of their disease as more disabling or burdensome [Suarez-Almazor *et al.*, 2007]. The evaluation of SSc severity and its impact on activities of daily living requires several measures due to multiple organ involvement; single organ outcome measures only provide limited information [Steen and Medsger, 1997].

The HAQ is one of the most commonly used measures of disability in musculoskeletal disorders and is also used in SSc as a simple, inexpensive and practical way to reflect the patient perspective [Bruce *et al.*, 2003a, 2005; Johnson *et al.*, 2005; Pope, 2011]. The HAQ is a self-reported questionnaire consisting of twenty questions split across eight domains, addressing rising, eating, walking, hygiene, dressing, reach, grip and usual activities [Bruce *et al.*, 2003b]. The HAQ was extended to form the SHAQ, a more disease-specific disability scale that incorporates the HAQ and five scleroderma related VAS into one score [Steen and Medsger, 1997]. The five VASs in the SHAQ assess the level of impairment due the complications frequently observed in SSc outside the musculoskeletal system, namely RP, DUs, gastrointestinal symptoms, respiratory symptoms, as well as the overall severity of the disease from the patient's perspective [Steen and Medsger, 1997]. The SHAQ is a reliable and valid measure of functional disability in SSc [Steen and Medsger, 1997; Merkel *et al.*, 2002; Smyth *et al.*, 2003; Johnson *et al.*, 2005; Pope, 2011].

Several studies have assessed the impact of selected SSc-specific symptoms on patients' life [Franck-Larsson *et al.*, 2009; Mouthon *et al.*, 2010; Omair *et al.*, 2012; Hughes *et al.*, 2015; Racine *et al.*, 2016], or assessed overall QoL or functional disability and factors associated with it [Smyth *et al.*, 2003; Hudson *et al.*, 2009; Strickland *et al.*, 2012]. However, due to the rarity

of the disease, most of these studies have a limited sample size and focus on sub-populations, for example only patients with DUs or patients with pulmonary hypertension [Chow *et al.*, 2008; Strickland *et al.*, 2012; Guillevin *et al.*, 2013; Lumetti *et al.*, 2015]. Recently, one large internet-based survey assessed patients' perception on factors impacting on the daily lives, as well as health related quality of life [Frantz *et al.*, 2016]. This study however was a purely patient based survey with no linkage to clinical data.

Our aim was therefore to prospectively analyse functional disability in a large cohort of SSc patients not selected for a particular organ manifestation, and to identify clinical factors contributing to impairment.

METHODS

Study population and design

The DeSScipher ("to decipher the optimal management of systemic sclerosis" [*The DeSScipher Project*, 2013; Frerix *et al.*, 2015]) project is a multinational, longitudinal study embedded in the EUSTAR group database [Walker *et al.*, 2007; Meier *et al.*, 2012]. The DeSScipher project consists of five observational trials focusing on DU, hand arthritis, interstitial lung disease, pulmonary hypertension and severe heart disease. However, DeSScipher patients as such are not selected for any specific organ manifestations as the DeSScipher cohort consists of EUSTAR patients being followed at DeSScipher centres during the DeSScipher project regardless of organ manifestations and eligibility into any of the DeSScipher observational trials (please see the DeSScipher website for more detail [*The DeSScipher Project*, no date]).

DeSScipher data were collected prospectively in a multicentre approach. Data collection for the DeSScipher project started in March 2013, however the recording of the SHAQ within the DeSScipher database only started in October 2014, and was independent of particular organ manifestations, SSc treatments or eligibility for a specific DeSScipher observational trial. Data for this study were exported in August 2016. Each DeSScipher centre obtained ethical approval by

its local ethics committee; written informed consent according to the declaration of Helsinki was required from each patient prior to enrolment.

All patients had to fulfill either the 1980 ACR criteria for SSc, or the 2013 ACR/EULAR criteria and were eligible for this analysis if they were above 18 years of age and had at least one SHAQ available [Masi *et al.*, 1980; Steen and Medsger, 1997; van den Hoogen *et al.*, 2013]. Patients were classified as diffuse or limited SSc depending on the most severe skin involvement at the time of the study visit or any prior visit.

The HAQ built into the SHAQ has a recall period of seven days, ranges from 0 to 3 and is categorised into mild to moderate difficulty (score of 0 to <1), moderate to severe disability (score of 1 to <2) and severe to very severe disability (score of 2 to 3) [Bruce *et al.*, 2003b, 2003a]. The VAS scales in the SHAQ assess the interference of the disease with daily activities and range from 0 (not limiting activities) to 100 (very severe limitation). In the original version of the SHAQ no combined score was built, instead the HAQ and the five VAS were assessed separately [Steen and Medsger, 1997]. Georges *et al*. proposed to average the eight HAQ categories and the five VASs (each downscaled to range from 0 to 3) into a composite SHAQ score ranging from 0 to 3 [Georges *et al.*, 2005]. For this cross-sectional study, the first SHAQ recorded was analysed.

Statistical analysis

Depending on the categorical or continuous nature of the variables, frequencies and percentages or means and SD were calculated. For categorical variables, between group comparisons were carried out using X^2-tests or Fisher's exact tests; t-tests were used for continuous variables. Missing data of covariates were imputed using multiple imputations by chained equations [Sterne *et al.*, 2009; Carpenter *et al.*, 2013].

After defining possible predictors of functional disability *a priori* (Table 8), predictors were identified using univariable and multivariable linear regression analyses. We decided not to include the SSc subset of the patients and sclerodactyly in the multivariable model, as these variables are strongly related to the mRSS.

Table 8. Description of possible predictors selected *a priori* for the analysis.

Demographics
- Age (years)
- Sex (female/male)

Disease characteristics
- Time since RP onset (years)
- Time since first non-RP manifestation (years)
- Modified Rodnan skin score (mRSS; range 0 to 51)
- Oesophageal symptoms (yes/no; dysphagia, reflux according to patient)
- Stomach symptoms (yes/no; early satiety, vomiting according to patient)
- Intestinal symptoms (yes/no; diarrhoea, bloating, constipation according to patient)
- Any gastrointestinal symptoms (yes/no; any of oesophageal, stomach or intestinal symptoms)
- Number of gastrointestinal symptoms (range 0 to 3; oesophageal, stomach and/or intestinal symptoms)
- Dyspnoea (modified NYHA functional class I to IV;
  - Class I: No limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea (shortness of breath).
  - Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in dyspnoea.
  - Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes dyspnoea.
  - Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest.)
- Puffy fingers (yes/no; current scleredema)
- Digital ulcers (yes/no; current ulcers distal to or at the proximal interphalangeal joint)
- Telangiectasia (yes/no)
- Joint synovitis (yes/no; by rheumatologist's judgement)
- Joint contractures (yes/no; by rheumatologist's judgement)
- Muscle weakness (yes/no; by rheumatologist's judgement defined as a paresis unexplained by a neuropathy or contracture)
- Muscle atrophy (yes/no; by rheumatologist's judgement)
- Fibromyalgia (yes/no; by rheumatologist's judgement)
- Systolic pulmonary artery pressure (PAPsys, mmHg; as estimated by echocardiography)
- Single breath diffusing capacity for carbon monoxide (DLCO, % of predicted)
- Forced vital capacity (FVC, % of predicted)
- Lung fibrosis on HRCT (yes/no)
- Conduction blocks (yes/no; AV-block, bundle branch blocks)
- Diastolic dysfunction (yes/no)
- Pericardial effusion (yes/no)
- Left ventricular ejection fraction (LVEF, %)

Laboratory
- Anticentromere autoantibodies positivity (ACA; yes/no)
- Anti-topoisomerase autoantibodies positivity (anti-Scl-70; yes/no)
- Anti-RNA polymerase-III autoantibodies positivity (anti-RNAP-III; yes/no)
- Erythrocyte sedimentation rate (ESR; mm/hour)
- Serum creatinine kinase elevation (CK; yes/no)

To compare levels of disability in patients with diffuse SSc and limited SSc we reduced the original model to factors that were strong and clinically significant predictors of functional disability in the overall patient group or were defined *a priori*.

The MCID of the HAQ is stated to be ≥0.22 [Wells *et al.*, 1993]. As the SHAQ is based on the HAQ and has the same range, we applied this threshold also to the SHAQ. We treated a difference of ≥10mm as the MCID for the VAS components [Wells *et al.*, 1993; Dworkin *et al.*, 2008; Strand *et al.*, 2011].

All analyses were performed with Stata/IC 13.1 (StataCorp, Texas, USA).

RESULTS

Patient characteristics

At the time of the data export, 944 (38%) of the 2,488 adult DeSScipher patients had a SHAQ score. During the time of the SHAQ collection, 2084 patients had a visit after the introduction of the SHAQ, therefore 45% of eligible patients had a SHAQ score available. The demographic and disease characteristics of this study population are listed in Table 9.

Of the 944 patients, 115 (12.2%) fulfilled only the 2013 ACR/EULAR criteria but not the 1980 ACR classification criteria for SSc. Patients included in the study were of similar age and sex distribution as the patients excluded for the lack of a SHAQ. Additionally, both groups had comparable disease durations and SSc subset distributions (data not shown).

Table 9. Demographic and disease characteristics of the study population at the time of SHAQ assessment (n=944).

Characteristics of the study population (N=944)		% or mean (SD)
Age; years		56.8 (13.0)
Male sex		15.0
Disease characteristics		
Time since RP onset; years		14.8 (11.9)
Time since first non-RP manifestation; years		11.5 (9.1)
mRSS		6.7 (7.1)
Cutaneous involvement	Sine	6.9
	Limited	56.5
	Diffuse	36.6
Oesophageal symptoms		62.7
Stomach symptoms		26.6
Intestinal symptoms		38.1
Dyspnoea (modified NYHA functional class)	I	44.0
	II	47.4
	III	7.4
	IV	1.2
Sclerodactyly		72.5
Puffy fingers		42.8
Digital ulcers		13.2
Telangiectasia		74.9
Joint synovitis		11.4
Joint contractures		50.5
Tendon friction rubs		4.6
Muscle weakness		16.7
Muscle atrophy		6.7
Fibromyalgia		4.0
Conduction blocks		17.7
Diastolic dysfunction		45.2
Pericardial effusion		1.8
LVEF; %		62.2 (5.4)
LVEF <50%		1.3
PAPsys; mmHg		29.8 (12.1)
PAPsys >40mmHg		10.6
DLCO; % of predicted		63.3 (19.3)
FVC; % of predicted		94.8 (21.5)
FVC <80% of predicted		23.3
Lung fibrosis on HRCT		59.8
Laboratory parameters		
ANA positive		98.2
ACA positive		38.7
Anti-Scl-70 positive		48.4
Anti-RNAP-III positive		6.2
ESR; mm/hr		19.8 (16.0)
Creatinine kinase elevation		6.4

Functional disability

The mean SHAQ score was 0.87 (SD 0.66). 59.5% of the patients were in the lowest SHAQ category (score of 0 to <1), 34.0% had a score of 1 to <2 and 6.5% were in the category regarded as 'severe to very severe disability' (score of 2 to 3). Patients fulfilling only the 2013 ACR/EULAR criteria but not the 1980 ACR criteria had a lower average SHAQ score (0.55, SD 0.56) than patients fulfilling the 1980 ACR classification criteria (0.91, SD 0.66; p<0.001). Patients with diffuse cutaneous SSc had a higher mean SHAQ score (0.96, SD 0.65), than patients with limited SSc (0.83, SD 0.67; p=0.005). 46.8% of patients with diffuse SSc had mild to severe disability (score 1 to 3) compared to 37.6% with limited SSc (p=0.003).

The mean HAQ score was 0.92 (SD 0.78). 53.8% of patients fell into the 'mild to moderate difficulty' category (score <1), 34.1% into the 'moderate to severe disability' (score ≥1 to <2) and 12.1% into the 'severe to very severe disability' (score ≥2) category. Patients with diffuse SSc had a higher mean HAQ score than patients with limited SSc (1.04, SD 0.77 *vs.* 0.87, SD 0.77; p=0.002).

Of the five VASs included in the SHAQ, the highest values were reported on the overall disease severity VAS (mean 37mm, SD 27). Patients with diffuse SSc reported a higher level of limitation due to overall disease severity (mean 40mm, SD 27) than patients with limited SSc (mean 35mm, SD 27; p=0.02).

With respect to RP, the mean VAS impairment reported was 31mm (SD 28). Patients with diffuse SSc reported a higher level of impairment due to RP (mean 34mm, SD 29) than patients with limited SSc (mean 29mm, SD 27; p=0.01).

The average perceived limitation due to pulmonary problems was 24mm (SD 27). Patients with diffuse SSc reported a similar level of impairment due to pulmonary symptoms (mean 24mm, SD 27) as patients with limited SSc (mean 24mm, SD 28; p=0.81). Patients in higher modified NYHA functional classes (as a proxy for dyspnoea, please see **Table 8**) perceived a more marked pulmonary limitation than patients in modified NYHA-class I (modified NYHA-class IV, mean 74mm, SD 24; modified NYHA-class III, mean 61mm, SD 24; modified NYHA-class II, mean 29mm, SD 26; modified NYHA-class I, mean 11mm, SD 19; p<0.001).

With respect to gastrointestinal problems, patients reported a VAS average of 20mm (SD 26). There was no difference in the perceived impairment due to gastrointestinal problems between patients with diffuse SSc (mean 18mm, SD 25) and limited SSc (mean 21mm, SD 27; p=0.11). Patients with a higher number of simultaneous gastrointestinal symptoms reported higher average VAS scores than patients with a low number of gastrointestinal symptoms (42mm, SD 31 for patients reporting all of oesophageal, gastric and intestinal symptoms; 26mm, SD 26 for patients reporting symptoms in two gastrointestinal regions; 16mm, SD 23 for patients reporting symptoms in only one gastrointestinal region; *vs.* 7mm, SD 14 for patients reporting no gastrointestinal symptom, respectively; p<0.001).

The VAS assessing the impairment due to the presence of DU had relatively low scores (mean 19mm, SD 28). Patients with diffuse SSc (mean 22mm; SD 30) reported a higher level of impairment than patients with limited SSc (mean 18mm, SD 27; p=0.02). However, patients who had DU prior to enrolment, but not at the time of SHAQ reporting, had a mean DU VAS of 21mm (SD 28), and patients suffering from DUs at the time of SHAQ completion reported a mean VAS of 53mm (SD 33; p<0.001).

Predictors of functional disability

We first assessed the association of variables with the SHAQ with univariable analysis. The strongest predictor of disability was dyspnoea. In patients with modified NYHA class IV the SHAQ score was on average 1.17 units (95%CI 0.80-1.53) higher than in patients with modified NYHA class I (modified NYHA class III - 0.88, 95%CI 0.73-1.04 and modified NYHA class II - 0.40, 95%CI 0.32-0.48 all *vs.* modified NYHA class I). Weaker, although still clinically important predictors were (in order of magnitude) muscle weakness (increase of 0.51 units, 95%CI 0.40-0.62), the presence of fibromyalgia (increase of 0.47 units, 95%CI 0.25-0.69) and the three variables referring to gastrointestinal involvement (gastric 0.41 units, 95%CI 0.32-0.50; oesophageal 0.38 units, 95%CI 0.29-0.46 and intestinal symptoms 0.34 units, 95%CI 0.25-9.42).

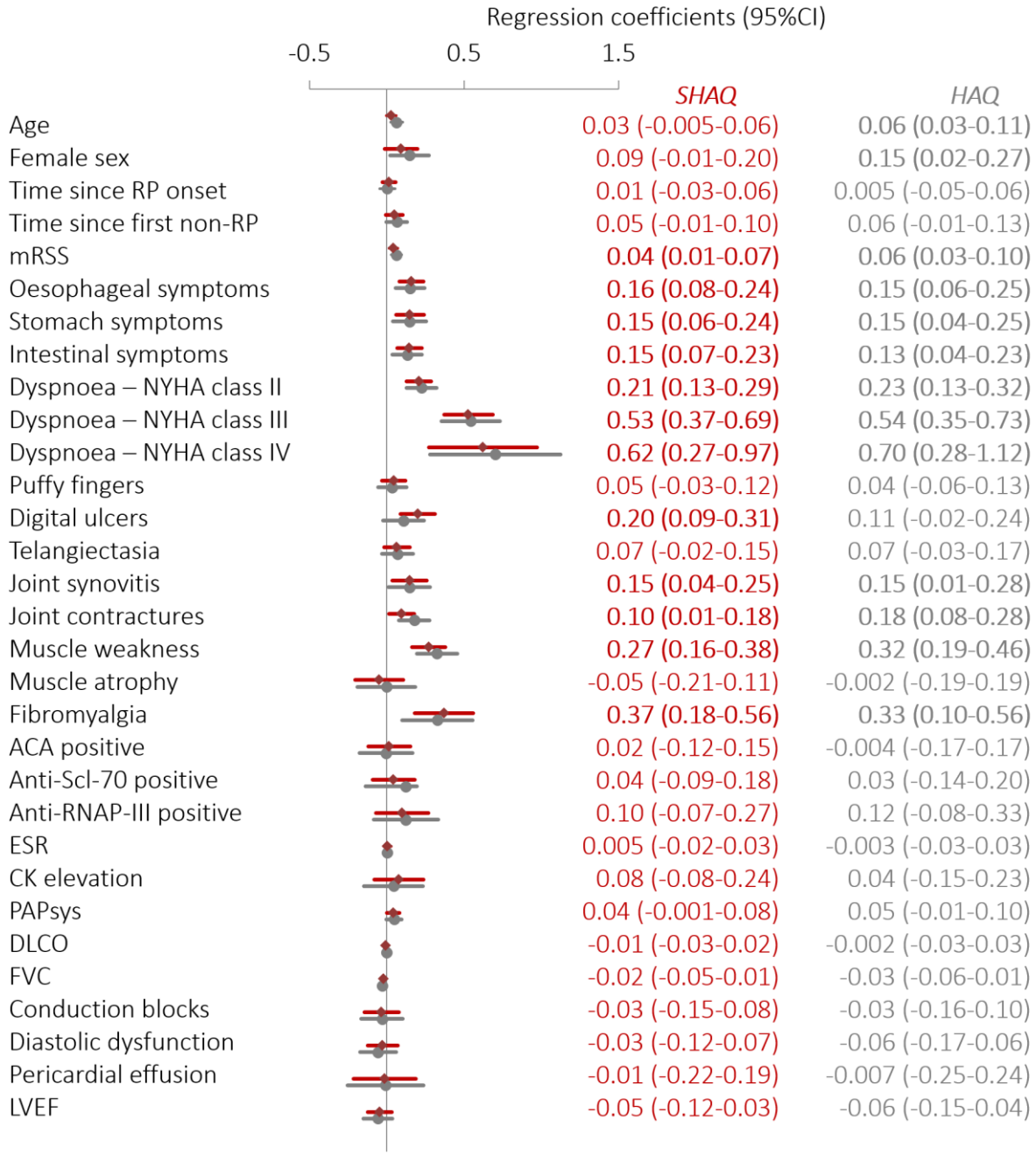
The multivariable analysis of the SHAQ was in line with the results observed in univariable analysis. Dyspnoea remained the strongest predictor of functional disability. The SHAQ scores reported by patients with modified NYHA class IV, III or II were on average 0.62 units, 0.53 units and 0.21 units higher than that of patients with modified NYHA class I (**Figure 16**). In addition,

both the presence of fibromyalgia as well as muscle weakness were associated with higher levels of disability. Patients with fibromyalgia reported on average a SHAQ value 0.37 units higher than that of patients without fibromyalgia, and patients experiencing muscle weakness recorded on average a 0.27 units higher SHAQ (**Figure 16**). Other factors contributing to disability included the presence of DUs, oesophageal, gastric and/or intestinal symptoms, joint contractures and a more severe skin involvement (**Figure 16**). Only dyspnoea, fibromyalgia and muscle weakness however remained clinically significant contributors to functional disability when applying the 0.22 threshold for the MCID [Wells *et al.*, 1993].

Patients experiencing any gastrointestinal involvement (presence of oesophageal, gastric or intestinal symptoms) reported a clinically significant higher SHAQ (0.24 units; 95%CI 0.15-0.32) than patients reporting no gastrointestinal involvement. In multivariable analysis, patients with multiple simultaneous gastrointestinal symptoms also had higher SHAQ scores than those featuring symptoms in only one or two regions of the gastrointestinal tract (oesophagus, stomach, or intestine). Patients reporting oesophageal, gastric and intestinal symptoms simultaneously had, on average, a SHAQ score of 0.46 units (95%CI 0.34-0.58) higher than patients reporting no gastrointestinal symptoms. Similarly, patients with symptoms in two or one gastrointestinal regions also reported a higher functional disability than patients with no gastrointestinal problems (0.28 units, 95%CI 0.18-0.38 and 0.13 units, 95% CI 0.04-0.22; respectively).

The analysis of the HAQ scores showed impairment similar to the SHAQ. In univariable analysis in patients in modified NYHA functional class IV the HAQ was on average 1.32 units higher (95%CI 0.88-1.75) than in patients in modified NYHA class I; respective values for patients in modified NYHA class III were 0.96 units (95%CI 0.78-1.14) and in patients in modified NYHA class II 0.46 units (95%CI 0.37-0.56 all *vs.* modified NYHA I). Other factors associated with higher HAQ scores were (in order of magnitude): the presence of muscle weakness (0.59 units [95%CI 0.46-0.72]), the presence of muscle atrophy (0.50 units [95%CI 0.30-0.70]), the presence of fibromyalgia (0.42 units [95%CI 0.16-0.67]), joint contractures (0.44 units [95%CI 0.35-0.54]), gastrointestinal symptoms (oesophageal-0.40 units, 95%CI 0.30-0.50; gastric-0.43 units, 95%CI 0.32-0.54; intestinal-0.35 units, 95%CI 0.25-0.45) and tendon friction rubs (0.40 units [95%CI 0.16-0.64]).

Figure 16. Predictors for the composite SHAQ and the HAQ scores in SSc patients.
Multivariable regression coefficients with 95%CI for the composite SHAQ and the HAQ scores (both ranging from 0 to 3). Regression coefficients and their 95%CI are presented in bold writing if the 95%CIs do not include zero.
Age, increase per 10 years; DLCO, increase per 10% of predicted; dyspnoea, modified NYHA functional classes II/III/IV *vs.* LVEF, increase per 10%; modified NYHA functional class I; ESR, increase per 10mm/hr; FVC, increase per 10% of predicted; mRSS, increase per 5 points; PAPsys, increase per 10mmHg; sex, female *vs* male; time since first non-RP, increase per 10 years; time since RP onset, increase per 10 years; all others, yes/no.



None of the objective clinical measures were associated with a higher SHAQ score (Figure 16). The changes in the average SHAQ scores were (in order of absolute magnitude): 10% higher LVEF (-0.05 units), 10mmHg higher PAPsys (0.04 units), presence of conduction blocks (-0.04 units), presence of a diastolic dysfunction (-0.03 units), 10% of predicted FVC (-0.02 units), 10% of predicted lower DLCO/sb (-0.01 units) and the presence of pericardial effusion (-0.01 units).

In multivariable analyses, patients with modified NYHA functional class IV had an average HAQ score of 0.70 units higher than patients with modified NYHA functional class I (modified NYHA class III - 0.54 units, modified NYHA class II - 0.23 units all *vs.* modified NYHA class I). The presence of fibromyalgia (increase of 0.33 units) as well as of muscle weakness (increase of 0.32 units) were also strong and clinically important predictors of elevated HAQ scores (Figure 16). The presence of any gastrointestinal problems, i.e. either the presence of oesophageal, stomach or intestinal symptoms, led to a clinically important average increase of 0.22 HAQ units (95%CI 0.11-0.31). Similarly, the number of simultaneous gastrointestinal symptoms was a strong predictor of an elevated HAQ; patients reporting each of oesophageal, gastric and intestinal symptoms, the average HAQ increase was 0.44 units (95%CI 0.30-0.58), for patients reporting symptoms in two gastrointestinal regions the average increase was 0.26 units (95%CI 0.14-0.38) and for patients reporting symptoms in only one gastrointestinal region the HAQ increase was 0.11 units (95%CI 0.002-0.22) compared to patients reporting no gastrointestinal symptom.

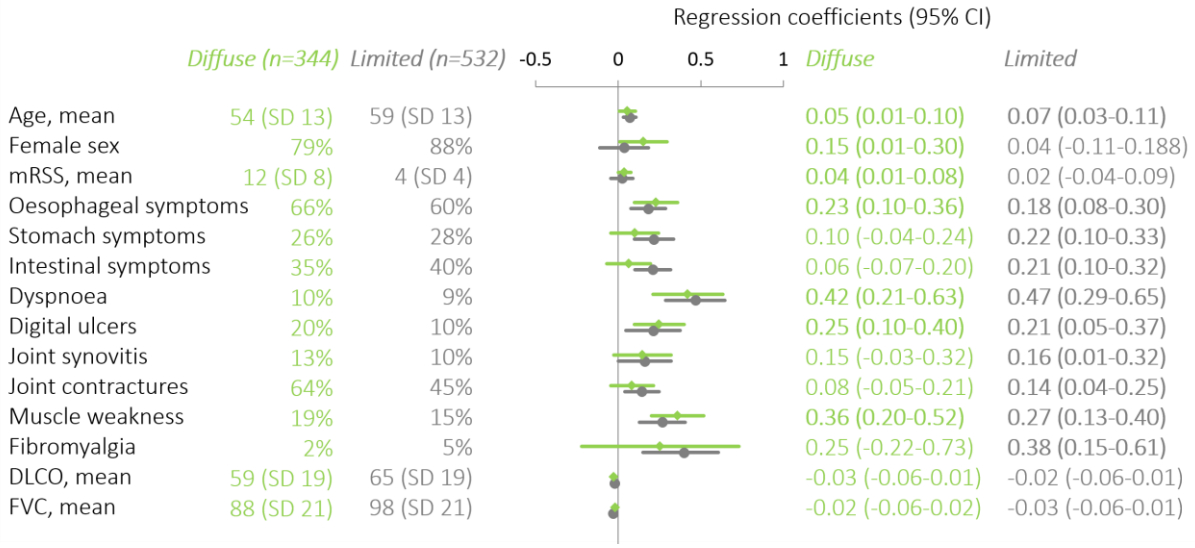
Disability in the SSc subsets

In patients with diffuse SSc (n=344), the factors contributing to a clinically meaningful SHAQ increase were similar to those contributing in patients with limited SSc (n=532; Figure 17), namely dyspnoea (modified NYHA III/IV vs. modified NYHA I/II increase of 0.42 units), muscle weakness (increase of 0.36 units) and gastrointestinal symptoms (Figure 17). Patients with fibromyalgia also had on average a 0.25 units higher SHAQ (Figure 17).

In both SSc subsets, the presence of multiple simultaneous gastrointestinal symptoms also strongly predicted disability. In patients with diffuse SSc, the SHAQ was on average 0.39 units (95%CI 0.19-0.59) higher in patients simultaneously reporting oesophageal, gastric and

intestinal symptoms than in patients not reporting gastrointestinal symptoms. In the group of patients with limited SSc, this difference was even greater (0.60 units (95%CI 0.44-0.78)).

Figure 17. Predictors for the composite SHAQ in patients with diffuse and patients with limited cutaneous SSc.
Demographic and disease characteristic as well as multivariable regression coefficients with 95% CI for the composite SHAQ score (range 0 to 3) for patients with diffuse and limited cutaneous SSc. Regression coefficients and their 95%CI are presented in bold writing if the 95%CIs do not include zero.
Age, increase per 10 years; DLCO and FVC, increase per 10% of predicted; dyspnoea, modified NYHA functional class III/IV *vs.* modified NYHA functional class I/II; mRSS, increase per 5 points; all others, yes/no.



DISCUSSION

Our study is by far the largest study linking patients' self-assessed disability with objective clinical data and is also the first study of its size to analyse a comprehensive set of clinical factors contributing to disability in an SSc population not selected for a particular organ manifestation or subset. The physicians' main attention while caring for SSc patients is often focused on

objective measures of function for example pulmonary function tests. These measures may however not reflect the patient's experience with the disease, self-perceived impact on QoL and functional capacity.

The most important factors predicting functional disability in our study were dyspnoea, gastrointestinal symptoms, fibromyalgia, muscle weakness and the presence of DU, in line with the results of smaller studies [Suarez-Almazor *et al.*, 2007; Franck-Larsson *et al.*, 2009; Omair *et al.*, 2012; Guillevin *et al.*, 2013; Lóránd *et al.*, 2014; Brand *et al.*, 2015; Lumetti *et al.*, 2015]. Thus, there is a major difference between the factors driving patient perceived levels of disability and those emphasized by physicians (i.e. lung function testing, pulmonary arterial pressure estimates et cetera). In clinical practice though, objective quantifications of gastrointestinal symptoms, fibromyalgia, muscle weakness and DUs are rarely performed. Comparing the four specific VASs, the highest patient-rated limitation of daily life was due to RP, followed by pulmonary and gastrointestinal symptoms. A similar finding was observed in two surveys in which SSc patients ranked RP, gastrointestinal complications, musculoskeletal involvements and pain among the symptoms influencing their daily life the most [Bassel *et al.*, 2011; Frantz *et al.*, 2016]. In contrast to our study, Strickland et al. [Strickland *et al.*, 2012] only found an association between functional disability and gastrointestinal involvement, but not with any other demographic or clinical variable. Similarly, Chow et al. [Chow *et al.*, 2008] did not detect a correlation between NYHA functional class, the strongest predicting factor in our study, and functional disability in SSc patients with pulmonary arterial hypertension. One likely reason for this discrepancy is the limited sample size of 68 and 41 patients, respectively. Additionally, in the study by Chow et al. [Chow *et al.*, 2008] the selection of patients might be another likely reason as the investigators only included SSc patients with pulmonary arterial hypertension and dyspnoea resulting in a distribution of NYHA classes skewed towards the higher classes.

The overall level of disability as identified by the HAQ in our European SSc population is more than 4 times higher than that reported in the general French population, and comparable with that reported in other systemic rheumatic diseases [Johnson *et al.*, 2006; Loos-Ayav *et al.*, 2007; Oude Voshaar *et al.*, 2014]. The HAQ score observed in our cohort is similar to that found in other SSc studies, with about half of patients considering themselves to be mildly to moderately disabled [Strickland *et al.*, 2012; Racine *et al.*, 2016]. However, the SHAQ scores as well as the

VASs encompassed in it are lower in our study than in a French single-centre study [Georges *et al.*, 2005]. This discordance might be explained by the lower percentage of diffuse SSc patients in our population.

In patients with diffuse SSc, the level of disability was significantly higher than in patients with limited SSc. The differences between SSc subsets in our cohort were however smaller than those reported previously in much smaller studies [Smyth *et al.*, 2003; Georges *et al.*, 2005; Strickland *et al.*, 2012]. Interestingly, the main factors contributing to disability, namely dyspnoea, gastrointestinal symptoms, muscle weakness, DUs and pain, were similar in the SSc subsets. This goes in line with a recent survey by Frantz et al [Frantz *et al.*, 2016] which identified no difference of patient perceived impact of organ involvement on QoL between SSc subsets.

There are limitations of our study. We only had SHAQ data of about 45% of all eligible patients. A selection bias might have occurred in both directions, i.e. patients with more severe disease may have felt too unwell to fill in the SHAQ questionnaire, or were actually more likely to fill in the questionnaire, as they felt more impaired. The demographic characteristics of the patients included in this study were however comparable to the DeSScipher patients without an available SHAQ, as were the disease duration and the distribution of the SSc subsets. One problem often arising in observational studies is the data quality. However, one big strength of the DeSScipher cohort is that there were various strategies in place to enhance data quality, including on-site data monitoring. Thus, our results are likely to better reflect the bigger SSc community than those of previous studies, particularly due to the multi-centre and multinational nature of this study.

In conclusion, this study demonstrates significantly impaired functional capacity in a large proportion of SSc patients, and demonstrates that dyspnoea, pain, DUs, muscle weakness and gastrointestinal symptoms are the most important contributors perceived by the patients. Our finding that objective measures are not associated with patient perceived disability is a clarion call to researchers and clinicians that the many and multi-faceted aetiologies of disability in SSc are poorly understood. Further, the root causes impacting disability are likely overlooked and poorly assessed in the clinical setting, As a result of this, QoL is not yet targeted by our treatment armamentarium.

7. DISCUSSION, CONCLUSION AND OUTLOOK

7.1. SUMMARY OF MAIN FINDINGS

This thesis sheds light on the timing of SSc specific organ manifestations and risk factors for speedier onsets, the effect of the modifiable risk factor, smoking, on organ manifestations and factors that the patients perceive as most burdensome. The main findings of this thesis are summarised below.

Aim 1 - Organ Involvement, when does it start?

This longitudinal study uniquely mapped the incidence of skin and organ manifestations in early SSc patients and detailed differences in the evolution of disease manifestations. The main findings are that early after the onset of RP, organ manifestations exhibit rapid kinetics in SSc. Most patients experience the maximal gain of skin sclerosis within one year after the onset of RP and diffuse cutaneous involvement emerges newly in only a minority of patients after five years of disease onset. In every internal organ system, half of all organ manifestations are evident within the first two years. The disease onset follows a simultaneous rather than sequential manifestation pattern, i.e., the steep increase in manifestations during the first years is persistently observed across the studied organ complications. Even the severe complications, for instance, PH and ILD, are not restricted to late disease contrasting the experienced-based knowledge about the timing of manifestation until now (Figure 2 *[Varga et al*., 2012]).

The different risk factors for the occurrence of the various organ manifestations modify the cumulative incidences of the organ manifestations. However, these do not substantially modify the steep increase in manifestation rates during the first two years after RP onset. For example, the risk factors governing the extent and severity of skin involvement (e.g., male sex and autoantibody status associated with the development of diffuse disease) do not influence the disease kinetics, e.g., the time to mRSS peaking.

The main finding that early after the onset of RP, organ manifestations exhibit rapid kinetics in SSc, implies that there is only a short 'window of opportunity' to prevent incident organ damage. By mapping the temporal evolution of SSc specific manifestations and identifying risk

factors early during the disease course, this study will enable physicians to more accurately counsel SSc patients presenting early in their disease. These findings also have implications for the design of new diagnostic strategies and therapeutics aimed to 'widen' the still very narrow 'window of opportunity'.

Aim 2 - Smoking, does it make it worse?

This study assessed possible associations of smoking exposure and smoking intensity with organ manifestations and their level of worsening. It goes beyond those already published not only by the number of patients included, but also by applying three different smoking models leading to greater robustness of the results. We found that the known adverse effects of smoking on bronchial airways and alveoli are also observed in SSc patients. The main finding is, however, that there are no robust adverse effects of smoking on the progression of SSc-specific pulmonary or cutaneous manifestations.

We also found a lower prevalence of anti-Scl-70 autoantibodies in current smokers. This imbalance was also seen in another publication [Chaudhary *et al.*, 2011] and raises the question of a possible aetiopathological link between smoking and anti-Scl-70 positivity.

The findings of this study argue against a major role of tobacco-associated free radicals, vasoconstrictory and immunomodulatory effects in the pathogenesis of SSc vasculopathy and fibrosis. The results are of importance firstly to clinicians who counsel and manage SSc patients, but also to the patients themselves wondering about the effect of the modifiable risk factor smoking on their disease outcome.

Aim 3 - Physical function, the patient perspective.

The physician's main attention while caring for SSc patients is often focused on objective measures of function. These measures, however, may not reflect the patients' experiences with the disease and their self-perceived impact on their functional abilities. Therefore, this study assessed functional disability and identified factors contributing to functional impairment. The

main finding is that there is a major difference between the factors driving patient perceived levels of disability and those emphasized by physicians in the evaluation of their disease.

Patients perceive dyspnoea, GI symptoms, pain, muscle weakness and the presence of DUs as the main factors driving their level of disability. In clinical practice though, objective quantifications of GI symptoms, fibromyalgia, and muscle weakness are rarely performed, and therefore the causes influencing disability are likely overlooked and poorly assessed in the clinical setting. Moreover, as a result of this, QoL and functional ability are not targeted by the current treatment armamentarium. This study found that objective measures are not associated with patient-perceived disability and, is, therefore, a clarion call to researchers and clinicians that the many and multi-faceted aetiologies of disability in SSc are poorly understood.

7.2. STRENGTH AND LIMITATIONS

The greatest strengths of all four studies are their large sample sizes, the multinational nature, and their unselected patient populations, i.e., their registry-based design. At the same time, this great strength, i.e., the registry-based set-up, also poses certain limitations. As in almost all registries, data completeness and data quality are also issues within the EUSTAR/DeSScipher registry. However, various strategies are in place to minimise these problems. Plausibility, validity, range, and presence checks to improve data quality and to a certain extent also data completeness were already implemented into the EUSTAR registry from the beginning of the online data collection. These were greatly extended during the DeSScipher do-over of the database as extensive checks at the data entry level are among the most essential tools to improve data quality in almost all data collection systems especially in registries [Silver *et al.*, 2006; Gliklich *et al.*, 2014]. Additionally, at DeSScipher centres on-site as well as off-site monitoring with source data verification took place to enhance the quality of data as well as their completeness further.

Another problem is the data reliability of the more ´subjective` measures such as the skin scoring for the mRSS. Reliable data on the level of skin involvement is especially important in SSc, firstly as it is a hallmark feature of the disease and secondly as it is an outcome measure of

two of the three main aims of this project. As the mRSS has a high intra-person variability, the centres were encouraged to always have the same physician carry out the skin scoring [Clements et al., 1995]. Additionally, EUSTAR offered repeated mRSS training courses to instruct the physicians, and there was also a training video available for physician who had not undergone one of the training courses to minimise the variability of the skin scoring [Czirják et al., 2007].

There are also potential study-specific limitations. In the first two studies assessing the speed of organ manifestation onset, some SSc patients had documented organ complications already at their baseline visit. In this case, we did not know the exact onset of the complication leading to an overestimation of the time to its onset. However, the longest possible overestimation is one year, as we restricted the patient population to those patients with a baseline visit within one year after the disease onset.

In the smoking study, the information on the smoking status and the smoking intensity was provided by the patients, and we had no means to verify this information. We were, however, able to demonstrate the known adverse effects of smoking, suggesting that the information provided by the patients was not random. A major strength of this study was also the utilisation of three smoking models assessing both the smoking behaviour and the smoking intensity as well as additionally the CSI of patients. Especially the use of the CSI incorporating smoking duration, time since smoking cessation and the smoking intensity into one score added to the robustness and the validity of the results.

7.3. GENERALISABILITY OF FINDINGS

*T*he EUSTAR/DeSScipher patient population, *per se*, is an unselected cohort of patients, and therefore results are generalizable to SSc patients. However, we applied some restrictions to the populations we studied, either ´actively` by restricting the population to patients presenting early after disease onset (Aim 1) or patients with a follow-up in the required time frame (Aim 2) or ´passively` by just including patients with available data for the outcome measures of interest (Aims 2 and 3).

By restricting the included patients to patients presenting early after disease onset, we introduced a selection bias as evidenced by the high prevalence of male and anti-Scl-70 positive patients and also by their higher age of onset in those patients included in the study. These factors are known to be associated with more severe disease and adverse outcomes in SSc [Perera *et al.*, 2007; Walker *et al.*, 2007; Graf *et al.*, 2012; Nihtyanova *et al.*, 2014; Elhai *et al.*, 2016]. Hence, the generalizability to the entire SSc population is questionable. Nevertheless, more than half of all EUSTAR patients (i.e., the *entire EUSTAR cohort*) experienced their first non-RP feature of the disease within one year of the onset of RP (Figure 11). Therefore, the results are still generalizable to a rather high percentage of SSc patients.

In the smoking study (Aim 2), we only included patients with a follow-up visit. We are aware that this decision yields the risk of an informative drop-out whereby we might have excluded the sickest patients who might be most likely to have worsening disease and therefore enriched the studied population with ´healthier` patients or *vice versa* enriching for ´sicker` patients. However, we did compare the demographics and the disease characteristics of the patients excluded due to the absence of a follow-up visit to the included patients (Supplementary Table 6), and we did not see any major differences. Therefore, we did not exclude the sickest nor the healthiest patients by this inclusion criterion.

We also did not have smoking data on almost half of the adult EUSTAR SSc patients. Most of the missing data on smoking behaviour (around 98%) are purely a design issue as the smoking module was only introduced into EUSTAR in 2013. Therefore, those patients who were not included in the study due to the ´missing smoking data by design ` will be ´missing completely at random (MCAR)` and will not introduce a bias. Both points above do argue against a major selection bias, and therefore the results are generalizable to the entire SSc patient population.

Similarly, to the above inclusion criterion, we did the same for the functional disability study (Aim 3) where we only included patients who filled in the PRO questionnaire (around 45% of all eligible patients). The possible selection bias arising from this might have gone in both directions. Patients with severe disease might have been more likely to fill in the SHAQ questionnaire, as they felt more impaired. On the other hand, they might have been less likely as they were too unwell to fill in the PRO. Both scenarios would bias the results in different directions. However, from our experience and communications with other centres, the low ´compliance` was a mix of:

(1) the investigators not asking the patients to fill the SHAQs for various reasons (not enough time during clinic visits, being critical about PROs, just forgetting it, etc.) and

(2) patients not filling in the questionnaire also for various reasons (not wanting to fill in anything, just forgetting to do so, forgetting to return it, etc.).

Additionally, the demographic characteristics and the distribution of the SSc subsets of the patients included in the functional disability study were comparable to the patients without information on their functional ability. Therefore, we believe that this selection did not introduce a major bias and that the results are valid for unselected SSc populations.

7.4. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

A main clinical implication of these studies is that SSc patients need to be diagnosed early after disease onset, risk stratified and followed tightly with planned controls. This is important, especially early on in the disease, to ´catch` internal organ involvement in its incident stages, and because the more severe, potentially life-threatening complications of the disease are not limited to later disease. Additionally, awareness needs to be raised and improved among physicians for early referral of SSc patients or patients suspected to suffer from SSc to centres specialised in SSc care allowing to use the narrow 'window of opportunity` effectively as more than half of all organ complications manifest within the first two years of the disease. These results also enable the treating physicians to counsel and manage patients presenting early in the course of SSc more accurately regarding the expected speed of onset of organ manifestations and also to ´risk stratify` the patients for example according to their sex and autoantibody profile.

One factor that we did not include in the studies was the patients' race. It is known, that African Americans have a younger age at disease onset, have a more severe disease and greater mortality. Data, however, mostly stem from African Americans. Studies on the disease presentation and severity on Africans and especially Asians are sparse. In collaboration with EUSTAR and the EUSTAR centres in Johannesburg, South Africa, and Beijing, China, we recently initiated a study looking at differences in disease presentation and severity in these patient groups. This will help to ´risk stratify` patients even further.

The results that objective disease severity measures as assessed by the physicians do not correlate with patient-perceived disability, actually raise more questions than they provide firm answers; questions which should be essential to research priorities and the development of targeted strategies in clinical care. They indicate that both perspectives, the physicians' and the patients', should be taken into account as complementary and that the possible communication gaps between physicians and patients should be closed. The results are also a clarion call to researchers and clinicians by indicating that the many and multi-faced aetiologies of disability and QoL in SSc are poorly understood. Furthermore, the root causes impacting disability are likely overlooked and poorly assessed in the clinical setting and, as a result of this lack of knowledge, management strategies are not yet part of the treatment armamentarium. Aspects of QoL and disability are plentiful, everyday occurrences, making them more ´ordinary` and therefore easily overlooked opportunities to make it easier for the patient to live with the disease, in comparison to the anticipation of breath-taking novel drugs.

Current medical treatment of SSc patients is frustrated by the mediocre response of the disease. While the ultimate goal must be a low-risk curative therapy, people continue to live and die with the complex disease and with the heavy symptom burden of SSc. One of the high impacts clinicians and researchers might have in a patient’s health status in the next decade is to decipher and strategically address the barriers to function and quality of life, and potentially, survival.

To partially address this, we started a follow-up study focusing on the change in levels of functional ability over time and factors associated with an improvement as well as with worsening. Additionally, we would like to identify groups of patients with similar trajectories of functional ability over time and factors defining them to be able to put more emphasis on these factors, raise awareness, and hopefully treat them to help people living with SSc in their everyday life. We also aim to evaluate if changes in functional ability are associated with simultaneous worsening of organ manifestations, which also would enable the patients to be more involved in their disease management.

Research has tremendously increased the knowledge about SSc in the last decades, but it has not come far enough yet. Neither the exact cause of SSc nor all factors triggering disease onset and progression have been identified yet. Therefore, broad research is still required from basic,

translational and pharmaceutical partners, but also from large international cohorts and collaborations.

8. REFERENCES

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9. APPENDIX

LIST OF PEER-REVIEWED PUBLICATIONS RELATED TO THE THESIS

Sandmeier, B., **Jaeger, V. K.**, Nagy, G., Carreira, P. E., Tzankov, A., Widuchowska, M., Antic, M., Distler, O., Reichert, H., Distler, J. H. W., Walker, U. A. and Hügle, T. (2015) 'Autopsy versus clinical findings in patients with systemic sclerosis in a case series from patients of the EUSTAR database.', *Clinical and Experimental Rheumatology*, 33 Suppl 9(4), pp. 75–79.

Wirz, E.G.*, **Jaeger, V.K.***, Allanore, Y., Riemekasten, G., Hachulla, E., Distler, O., Airo, P., Carreira, P.E., Tikly, M., Vettori, S., Balbir Gurman, A., Damjanov, N., Müller-Ladner, U., Distler, J., Li, M., Häusermann, P.*, Walker, U.A.*, EUSTAR co-authors. (2016) 'Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis - A 10 year longitudinal study from the EUSTAR database', *Annals of the Rheumatic Diseases*, 75(7), pp. 1285-1292. doi: 10.1136/annrheumdis-2015-207271.

Jaeger, V. K. and Walker, U. A. (2016) 'Erectile Dysfunction in Systemic Sclerosis', *Current Rheumatology Reports*, 18(8). doi: 10.1007/s11926-016-0597-5.

Jaeger, V.K., Wirz, E.G., Allanore, Y., Rossbach, P., Riemekasten, G., Hachulla, E., Distler, O., Airo, P., Carreira, P.E., Balbir Gurman, A., Tikly, M., Vettori, S., Damjanov, N., Müller-Ladner, U., Distler, J.H.W., Li, M., Walker, U.A., EUSTAR co-authors. (2016) 'Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study', *PLoS ONE,* 11(10): e0163894. doi:10.1371/journal.pone.0163894.

Valentini, G., Iudici, M., Walker, U. A., **Jaeger, V. K.**, Baron, M., Carreira, P., Czirják, L., Denton, C. P., Distler, O., Hachulla, E., Herrick, A. L., Kowal-Bielecka, O., Pope, J., Müller-Ladner, U., Riemekasten, G., Avouac, J., Frerix, M., Jordan, S., Minier, T., Siegert, E., Ong, V. H., Vettori, S. and Allanore, Y. (2017) 'The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis: derivation and validation of a preliminarily revised EUSTAR activity index', *Annals of the Rheumatic Diseases*, 76(1), pp. 270–276. doi: 10.1136/annrheumdis-2016-209768

Beyer, C., Huscher, D., Ramming, A., Bergmann, C., Avouac, J., Guiducci, S., Meier, F., Vettori, S., Siegert, E., **Jaeger, V. K.**, Maurer, B., Riemekasten, G., Walker, U. A., Müller-Ladner, U., Valentini, G., Matucci-Cerinic, M., Allanore, Y., Distler, O., Schett, G. and Distler, J. H. W. (2018) 'Elevated serum levels of sonic hedgehog are associated with fibrotic and vascular manifestations in systemic sclerosis', *Annals of the Rheumatic Diseases*, 77(4), pp. 626–628. doi: 10.1136/annrheumdis-2016-210834.

Keck, A., **Jaeger, V. K.** and Walker, U. (2017) 'Myositiden bei Systemischer Sklerose, Lupus und Sjögren-Syndrom bei Kollagenosen', *Aktuelle Rheumatologie*, 42(4), pp. 310–315. doi: 10.1055/s-0042-112361. doi: 10.1055/s-0042-112361.

Jaeger, V.K., Distler, O., Maurer, B., Czirják, L., Lóránd, V., Valentini, G., Vettori, S., Del Galdo, F., Abignano, G., Denton, C., Nihtyanova, S., Allanore, Y., Avouac, J., Riemekasten, G., Siegert, E., Huscher, D., Matucci-Cerinic, M., Guiducci, S., Frerix, M., Tarner, I.H., Garay Toth, B., Fankhauser, B., Umbricht, J., Zakharova, A., Mihai, C., Cozzi, F., Yavuz, S., Hunzelmann, N.,

Rednic, S., Vacca, A., Schmeiser, T., Riccieri, V., García de la Peña Lefebvre, P., Gabrielli, A., Krummel-Lorenz, B., Martinovic, D., Ancuta, C., Smith, V., Müller-Ladner, U., Walker, U.A. (2018) 'Functional disability and its predictors in systemic sclerosis: a study from the DeSScipher project within the EUSTAR group', *Rheumatology,* 57(3), 441-450. doi: 10.1093/rheumatology/kex182.

Jaeger, V.K., Valentini, G., Hachulla, E., Cozzi, F., Distler, O., Airó, P., Czirják, L., Allanore, Y., Siegert, E., Rosato, E., Matucci-Cerinic, M, Caimmi, C., Henes, J., Carreira, P.E., Smith, V., del Galdo, F., Denton, C., Ullman, S., de Langhe, E., Riccieri, V., Alegre-Sancho, J.J., Rednic, S., Müller-Ladner, U., Walker, U.A. on behalf of EUSTAR co-authors. (2018) 'Smoking in Systemic Sclerosis: a Longitudinal European Scleroderma Trials and Research Group Study', *Arthritis & Rheumatology.* doi: 10.1002/art.40557, *Epub ahead of print.*

Walker, U. A.*, Jaeger, V. K.*, Arlettaz, L., Banyai, M., Beron, J., Chizzolini, C., Gröchenig, E., Müller, R., Spertini, F., Villiger, P. and Distler, O. (2018) ´Prospective evaluation of the capillaroscopic skin ulcer index (CSURI) in clinical practice`, *Arthritis Research & Therapy*. *Accepted*.

Blagojevic, J., Bellando-Randone, S., Abignano, G., Avouac, J., Cometi, L., Czirják, L., Denton, C., Distler, O., Frerix, M., Guiducci, S., Huscher, D., Jaeger, V. K., Lóránd, V., Maurer, B., Nihtyanova, S., Riemekasten, G., Siegert, E., Valentini, G., Vettori, S., Walker, U .A., Allanore, Y., Muller Ladner, U., Del Galdo, F. and Matucci-Cerinic, M. ´Classification, categorisation and essential items for digital ulcer evaluation in systemic sclerosis: a DeSScipher/EUSTAR survey`, *Submitted.*

Jaeger, V. K., Lebrecht, D., Nicholson, A., Wells, A., Bhayani, H., Gazdhar, A., Tamm, M., Venhoff, N., Geiser, T. and Walker, U. A. ´Mitochondrial DNA mutations and respiratory chain dysfunction in idiopathic and connective tissue disease-related lung fibrosis`, *Submitted.*

Blagojevic, J., Abignano, G., Avouac, J., Cometi, L., Frerix, M., Bellando-Randone, S., Guiducci, S., Huscher, D., Jaeger, V. K., Lóránd, V., Maurer, B., Nihtyanova, S., Riemekasten, G., Siegert, E., Tarner, I. H., Vettori, S., Walker, U. A., Czirják, L., Denton, C. P., Distler, O., Allanore, Y., Müller-Ladner, U., Matucci-Cerinic, M., Del Galdo, F. and EUSTAR co-workers. ´Treatment of digital ulcers (DU) in systemic sclerosis (SSc) in expert tertiary centres: results from the analysis of the observational real-life DeSScipher study`, *Submitted.*

***** Shared first author/contributed equally

LIST OF PEER-REVIEWED PUBLICATIONS PUBLISHED DURING THE TIME OF THE THESIS BUT UNRELATED TO THE THESIS

Jaeger, V. K., Rüegg, R., Steffen, R., Hatz, C. and Bühler, S. (2015) ´Travelers With Immune-Mediated Inflammatory Diseases: Are They Different?`, *Journal of Travel Medicine,* 22(3), pp. 161–167. doi: 10.1111/jtm.12184.

Stuehler, C., Kuenzli, E., **Jaeger, V. K.**, Baettig, V., Ferracin, F., Rajacic, Z., Kaiser, D., Bernadini, C., Forrer, P., Weisser, M., Elzi, L., Battegay, M., Halter, J., Passweg, J. and Khanna, N. (2015) ´Immune reconstitution after allogeneic hematopoietic stem cell transplantation and association with occurrence and outcome of invasive aspergillosis`, *The Journal of Infectious Disease,* 212(6), pp. 959-967. doi: 10.1186/1471-2334-14-528.

Schindler, V. M., **Jaeger, V. K.**, Held, L., Hatz, C. and Bühler, S. (2015) ´Travel style is a major risk factor for diarrhoea in India: a prospective cohort study`, *Clinical Microbiology and Infection,* 21(7), pp. 676.e1-4. doi: 10.1016/j.cmi.2015.03.005.

Walker, U. A.*, **Jaeger, V. K.***, Chatzidionysiou, K., Hetland M. L., Hauge, E.-M., Pavelka, K., Nordström, D.C., Canhão, H., Tomšič, M., van Vollenhoven, R. and Gabay, C. (2016) ´Rituximab Done! What's Next in Rheumatoid Arthritis? - A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis`, *Rheumatology,* 55(2), pp. 230-236. doi: 10.1093/rheumatology/kev297.

Jaeger, V. K.*, Tschudin, N.*, Rüegg, R., Hatz, C. and Bühler, S. (2015) ´The elderly, the young and the pregnant traveler – a retrospective data analysis from a large Swiss Travel Center with a special focus on malaria prophylaxis and yellow fever vaccination`, *Travel Medicine and Infectious Disease,* 13(6), pp. 475-484. doi: 10.1016/j.tmaid.2015.10.001.

Mayorga, O., Bühler, S., **Jaeger, V. K.**, Bally, S., Hatz, C., Frösner, G., Protzer, U., Van Damme, P., Egger, M. and Herzog, C. (2016) ´Single Dose Hepatitis A Immunisation: 7.5 Year Observational Study in Nicaraguan Children to Assess Protective Effectiveness and Immune Memory`, *Journal of Infectious Diseases,* 214(10), pp. 1498-1506. doi: 10.1093/infdis/jiw411

Croce, E., Hatz, C., Visser, L., Jonker, E. F., **Jaeger, V. K.** and Bühler, S. (2017) ´Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation – a systematic review of randomized trials, observational studies and case reports`, *Vaccine,* 35(9), pp. 1216-1226. doi: 10.1016/j.vaccine.2017.01.048.

Jaeger, V. K., Hoffmann, H. M., van der Poll, T., Tilson, H., Seibert, J., Speziale, A., Junge, G., Franke, K., Vritzali, E., Hawkins, P. N., Kuemmerle-Deschner, J. and Walker, U. A. (2017) ´Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study`, *Rheumatology,* 56(9), pp. 1484-1491. doi: 10.1093/rheumatology/kex185.

Bühler S., Lang P., Bally, B., Hatz, C. and **Jaeger, V. K.** (2017) ´Stop Measles in Switzerland – The Importance of Travel Medicine`, *Vaccine,* 35(30), pp. 3760-3763. doi: 10.1016/j.vaccine.2017.05.042.

Walker, U. A.*, Müller, R. B.*, **Jaeger, V. K.**, Theiler, R., Forster, A., Dufner, P., Ganz, F. and Kyburz, D. (2017) ´Disease activity dynamics in rheumatoid arthritis: patients' self-assessment

of disease activity via WebApp`, *Rheumatology,* 56 (10), pp. 1707-1712. doi: 10.1093/rheumatology/kex229.

Kuenzli, E., Juergensen, D., Kling, K., **Jaeger, V. K.**, DeCrom, S., Steffen, R., Widmer, A. F., Battegay, M., Hatz, C. and Neumayr, A. (2017) ´Previous exposure in a high-risk area for travellers' diarrhoea within the past year is associated with a significant protective effect for travellers' diarrhoea. A prospective observational cohort study in travellers to South Asia`, *Journal of Travel Medicine,* 24(5), pp. 1-6. doi: 10.1093/jtm/tax056.

Lechtenboehmer, C., **Jaeger, V. K.**, Kyburz, D., Walker, U. A.* and Hügle, T.* (2018) ´Radiologic Progression of Distal Interphalangeal Joint Osteoarthritis in Patients with Concomitant Rheumatoid Arthritis`, *Arthritis & Rheumatology.* doi: 10.1002/art.40684, *Epub ahead of print.*

Bratu, V. A., Häusermann, P., Walker, U. A., Daikeler, T., Zubler, V., **Jaeger, V. K.**, Weber, U. and Studler, U. (2018) ´Do patients with skin psoriasis show have subclinical axial spondyloarthritis involvement on whole-body MRI?`, *Arthritis Care & Research.* doi: 10.1002/acr.23767, *Epub ahead of print.*

Bischof, A.*, **Jaeger, V. K.***, Collins, M. P., Hadden, R., Luqmani, R., Suppiah, R., Craven, A. and Daikeler, T. ´Prevalence and characteristics of peripheral neuropathy at disease onset in patients with ANCA associated vasculitides: data from the DCVAS study`, *Submitted.*

Bühler, S., **Jaeger, V. K**., Bannert, B., Brümmerhoff, C., Ciurea, A., Fleury, G., Franz, J., Gabay, C., Hagenbuch, N., Held, L., Herzog, C., Hasler, P., Kling, K., Müller, R., Siegrist, C.A., Villiger, P., Walker, U. A. and Hatz, C. ´Safety and immunogenicity of tetanus and diphtheria vaccination in patients with rheumatic diseases – a prospective multi-centre study`, *Submitted.*

***** Shared first author/contributed equally

EXPLANATION OF THE TITLE

The skin and its thickness

The registry and its data

The star and the sunflower

-

Bringing it all together

-

DeSSciphering Systemic Sclerosis

The title of this thesis can be broken down into its parts each referring to a component of this thesis.

- ´the skin and its thickness` refers to the disease under study, systemic sclerosis.
- ´the registry and its data, the star and the sunflower` refers to registry in which the data used in this thesis was collected, the European Scleroderma Trials and Research registry (EUSTAR). The ´star` refers to the logo of the EUSTAR registry which originates from a painting by Paul Klee who died of systemic sclerosis. The ´sunflower` refers to the logo of the DeSScipher project.
- ´bringing it all together` refers to the data analysis without which no results would be obtained.
- ´DeSSciphering systemic sclerosis` refers to the results presented in this thesis while being a play on words with the DeSScipher project.