TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Systemic Sclerosis and Localized Scleroderma in Finland

Saara Kortelainen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1962 | MEDICA – ODONTOLOGICA | TURKU 2026

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

SYSTEMIC SCLEROSIS AND LOCALIZED SCLERODERMA IN FINLAND

Saara Kortelainen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1962 | MEDICA – ODONTOLOGICA | TURKU 2026

University of Turku

Faculty of Medicine
Department of Internal Medicine
Doctoral Programme in Clinical Research

Supervised by

Adjunct Professor Laura Pirilä, MD, PhD
Department of Rheumatology
Turku University Hospital and
University of Turku
Turku, Finland

Adjunct Professor Johanna Huhtakangas, MD, PhD
Rheumatology
Kuopio University Hospital
Kuopio, Finland

Professor Veli-Matti Kähäri, MD, PhD
Department of Dermatology
University of Turku and
Turku University Hospital
Turku, Finland

Reviewed by

Docent Jaana Panelius MD, PhD
Dermatology and Venereology
University of Helsinki
Helsinki, Finland

MD, PhD, Ritva Peltomaa
Department of Medicine and Rheumatology
Helsinki University Hospital and
University of Helsinki
Helsinki, Finland

Opponent

Adjunct Professor Laura Huilaja, MD, PhD
Department of Dermatology
Medical Research Center
Oulu University Hospital
Research Unit of Clinical Medicine
University of Oulu
Oulu, Finland

ISBN 978-952-02-0624-6 (PRINT)
ISBN 978-952-02-0625-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2026

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Internal Medicine
SAARA KORTELAINEN: Systemic Sclerosis and Localized Scleroderma in Finland
Doctoral Dissertation, 134 pp.
Doctoral Programme in Clinical Research
April 2026

ABSTRACT

Systemic sclerosis (SSc) is a chronic autoimmune multiorgan disease with high mortality. Localized scleroderma, or morphea, is a rare autoimmune disorder characterised by inflammation and fibrosis of the skin. The aim of this study was to examine the incidence of SSc and its changes in Finland after introducing the new classification criteria in 2013, the causes and predictors of death among Finnish SSc patients, as well as the clinical features, comorbidities and treatments of morphea patients in Southwest Finland. The study population comprised SSc patients treated in the hospital districts of Southwest Finland and Northern Ostrobothia during the years 1996–2018, death certificates of deceased patients from both hospital districts during the years 2000–2020. For the study of morphea, the study population comprised patients with morphea in Southwest Finland between 2005 and 2020.

During a 20-year follow-up period divided into 5-year intervals, the incidence of SSc in Finland increased significantly utilising the most recent criteria, but not with the older ones. The increase was observed in the limited cutaneous systemic sclerosis (lcSSc) subgroup, suggesting that the more sensitive criteria identify milder disease forms. A considerable proportion of patients with SSc died as a direct consequence of the disease, in both the lcSSc and diffuse cutaneous systemic sclerosis (dcSSc) subtypes (33% and 52%, respectively). Cardiopulmonary complications were the most common SSc-related causes of death. Patients who died due to SSc were younger, and mortality occurred earlier in the disease course compared to patients who died from other causes. The identified prognostic factors were consistent with the previous findings in the literature.

In Southwest Finland, morphea showed two age-related incidence peaks, occurred more frequently in females, and its incidence did not increase. The coexistence of other autoimmune diseases, particularly thyroid and skin diseases, was common, while concurrent SSc was rare (1.9%). The risk of malignancy was not increased. Extracutaneous manifestations were more common among pediatric-onset patients than adult-onset patients. Methotrexate was the most commonly used systemic treatment, and both methotrexate and phototherapy benefitted the majority of treated patients. These retrospective studies provide valuable insights into two relatively rare autoimmune diseases and their frequencies, prognostic factors, and comorbidities. The results may support clinical decision-making. The identification of prognostic factors can guide patient follow-up and facilitate more targeted screening for organ involvement and comorbid conditions.

KEYWORDS: Systemic sclerosis, localized scleroderma, morphea, incidence, classification criteria, causes of death, co-morbidities

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Sisätautioppi
SAARA KORTELAINEN: Systeeminen skleroosi ja paikallinen skleroderma Suomessa
Väitöskirja, 134 s.
Turun kliininen tohtoriohjelma
Huhtikuu 2026

TIIVISTELMÄ

Systeeminen skleroosi (SSc) on krooninen autoimmuunipohjainen monielinsairaus, jonka kuolleisuus on korkea. Paikallinen skleroderma eli morfea on harvinainen autoimmuunisairaus, jolle on ominaista ihon tulehdus ja fibroosi. Tämän tutkimuksen tavoitteena oli selvittää systeemisen skleroosin ilmaantuvuutta ja sen muutoksia Suomessa uusien luokittelukriteerien käyttöönoton jälkeen vuonna 2013, kuolinsyitä ja kuolemaa ennustavia tekijöitä suomalaisilla potilailla sekä morfea-potilaiden kliinisiä piirteitä, liitännäissairauksia ja hoitoja Lounais-Suomessa. Tutkimusjoukko koostui SSc-potilaista, joita hoidettiin Lounais-Suomen ja Pohjois-Pohjanmaan sairaanhoitopiireissä vuosina 1996–2018 sekä molempien sairaanhoitopiirien vuosina 2000–2020 kuolleiden potilaiden kuolintodistuksista SSc diagnoosilla löydetyistä potilaista. Morfeaa koskevassa tutkimuksessa tutkimusjoukko koostui Lounais-Suomen morfea-potilaista vuosina 2005–2020.

Viisivuotisjaksoissa kahdenkymmenen vuoden seuranta-aikana systeemisen skleroosin ilmaantuvuus Suomessa kasvoi merkittävästi, kun käytettiin uusimpia kriteerejä, mutta ei vanhempia kriteerejä käyttäen. Kasvu havaittiin rajoittuneen systeemisen skleroosin (lcSSc) alaryhmässä. Tulos viittaa siihen, että herkemmät kriteerit mahdollistavat lievempien tautimuotojen tunnistamisen. Huomattava osa potilaista kuoli taudin suorana seurauksena sekä lcSSc- että diffuusin systeeminen skleroosin (dcSSc) -alatyypeissä (33 % ja 52 %). Sydän- ja keuhkokomplikaatiot olivat yleisimmät perussairauteen liittyvät kuolinsyyt. Systeemisen skleroosin vuoksi kuolleet potilaat olivat nuorempia ja kuolemantapaukset ilmaantuivat aikaisemmin sairauden aikana verrattuna potilaisiin, jotka kuolivat muista syistä. Tunnistetut ennustetekijät olivat yhdenmukaisia aiemmin kirjallisuudessa raportoitujen havaintojen kanssa.

Tulokset osoittivat, että Lounais-Suomessa morfealla on kaksi ikään liittyvää ilmaantuvuuden huippua ja se on yleisempi naisilla. Ilmaantuvuudessa ei havaittu kasvua. Muiden autoimmuunisairauksien, erityisesti kilpirauhasen ja ihon sairauksien, samanaikainen esiintyminen oli yleistä, kun taas samanaikainen systeeminen skleroosin esiintyminen oli harvinaista (1.9 %). Pahanlaatuisen kasvaimen riski ei ollut kohonnut. Ihon ulkopuoliset ilmentymät olivat yleisempiä lapsilla kuin aikuisilla. Metotreksaatti oli yleisimmin käytetty systeeminen hoito, ja metotreksaatti sekä valohoito olivat hyödyllisiä suurimmalle osalle hoidetuista potilaista. Nämä retrospektiiviset tutkimukset antavat arvokasta tietoa kahdesta suhteellisen harvinaisesta autoimmuunisairaudesta, niiden esiintyvyydestä, ennustetekijöistä ja liitännäissairauksista. Tulokset voivat tukea kliinistä päätöksentekoa. Ennustetekijöiden tunnistaminen mahdollistaa potilaiden seurannan kohdentamisen ja tehostaa elinvaurioiden sekä liitännäissairauksien seulontaa.

AVAINSANAT: Systeeminen skleroosi, paikallinen skleroderma, morfea, ilmaantuvuus, luokittelukriteerit, kuolinsyyt, liitännäissairaudet

Table of Contents

Abbreviations

ABA	Abatacept
ACA	Anticentromere antibody
ACEi	Angiotensin-converting enzyme inhibitor
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
AHA	Anti-histone antibody
AI	Artificial intelligence
AIH	Autoimmune hepatitis
ARB	Angiotensin II receptor blocker
ATA	Antitopoisomerase antibody
AZA	Azathioprine
BAL	Bronchoalveolar lavage
BNP	B-type natriuretic peptide
CAR	Chimeric antigen receptor
CCB	Calcium channel blocker
CCL18	CC Chemokine ligand 18
CHEST	American College of Chest Physicians
CMR	Cardiac magnetic resonance imaging
CMV	Cytomegalovirus
CT	Computed tomography
CTD	Connective tissue disease
CTGF	Connective tissue growth factor
CXCL4	Chemokine [C-X-C motif] ligand 4
CYC	Cyclophosphamide
dcSSc	Diffuse cutaneous systemic sclerosis
DM	Dermatomyositis
DLCO	Diffusing capacity of the lung for carbon monoxide
DPS	Digital pitting scar
DU	Digital ulcer
EBV	Epstein-Barr Virus
ECDS	En coup de sabre

ECG	Electrocardiogram
ECM	Extracellular matrix
EDF	European Dermatology Forum
EGD	Esophagogastroduodenoscopy
ELISA	Enzyme-like immunosorbent assay
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
EULAR	European League Against Rheumatism – The European Alliance of Association for Rheumatology
EUSTAR	European Scleroderma Trials and Research Group
FC	Functional class
FVC	Forced vital capacity
GAVE	Gastric antral vascular ectasia
GER	Gastroesophageal reflux
GI	Gastrointestinal
HCQ	Hydroxychloroquine
HEp-2	Human epithelial type -2
HRCT	High resolution computed tomography
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
IB	Immunoblotting
ICD	International Classification of Diseases
ID	Immunodiffusion
IIF	Indirect immunofluorescence
IL-6	Interleukin-6
ILD	Interstitial lung disease
IQR	Interquartile range
IVIG	Intravenous immunoglobulin
KL-6	Krebs von den Lungen -6
lcSSc	Limited cutaneous systemic sclerosis
LoSCAT	Localized Scleroderma Assessment Tool
LoSDI	Localized Scleroderma Damage Index
LSA	Lichen sclerosus et atroficus
LS	Localized scleroderma
MCTD	Mixed connective tissue disease
MHC	Major Histocompatibility Complex
mLOSSI	Modified Localized Skin Severity Index
MMF	Mycophenolate mofetil
mPAP	Mean pulmonary arterial pressure

MRI	Magnetic resonance imaging
mRSS	Modified Rodnan Skin Score
MTX	Methotrexate
NSIP	Nonspecific interstitial pneumonia
NT-proBNP	N-terminal prohormone BNP
NVC	Nailfold videocapillaroscopy
OCT	Optical coherence tomography
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PBC	Primary biliary cholangitis
PCA	Prostacyclin analogues
pDC	Plasma dendritic cell
PDE5i	Phosphodiesterase 5 inhibitor
PFT	Pulmonary function test
PH	Pulmonary hypertension
pHI	Primary heart involvement
PM	Polymyositis
PPI	Proton pump inhibitor
PRA	Prostacyclin receptor agonist
PRO	Patient reported outcome
PRS	Parry-Romberg Syndrome
PSC	Primary sclerosing cholangitis
PVR	Pulmonal vascular resistance
RA	Rheumatoid arthritis
RCM	Reflectance confocal microscopy
RCT	Randomised controlled trial
RF	Rheumatoid factor
RHC	Right heart catheterization
RNAPol3	RNA-polymerase 3
RP	Raynaud′s phenomenon
RTX	Rituximab
SD	Standard deviation
sGC	Soluble guanylate cyclase stimulator
SIBO	Small intestinal bacterial overgrowth
SjD	Sjögren′s disease
SLE	Systemic lupus erythematosus
SLS	Scleroderma lung study
SMR	Standardised mortality ratio
SPECT	Single photon emission computed tomography
SRC	Scleroderma renal crisis

SSc	Systemic sclerosis
ssSSc	Systemic sclerosis sine scleroderma
TCZ	Tocilizumab
TGFβ	Transforming growth factor β
T1-IFN	Type 1 Interferon
UCTD	Undifferentiated connective tissue disease
UIP	Usual interstitial pneumonia
US	Ultrasonography
VEDOSS	Very early diagnosis of systemic sclerosis

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kortelainen S, Käyrä M, Hurme S, Paltta J, Pirilä L and Huhtakangas J. Systemic sclerosis: Changes in the incidence rates in the Finnish population during the years 1999-2018. *Scandinavian Journal of Rheumatology*, 2024 Jan; 53(1):29–35.

II Kortelainen S, Käyrä M, Rissanen T, Paltta J, Taimen K, Pirilä L and Huhtakangas J. Causes and predictors of death among Finnish patients with systemic sclerosis. *Scandinavian Journal of Rheumatology*, 2024 Jul; 53(4):269–275.

III Kortelainen S, Hieta N, Rissanen T, Paltta J, Pirilä L and Kähäri V-M. Localized scleroderma and related comorbidities: a single-centre cohort study *British Journal of Dermatology*, 2026; 194:351–358.

1 Introduction

Systemic sclerosis (SSc) is a chronic rheumatic autoimmune disease, characterised by vasculopathy and fibrosis of the skin and internal organs. The severity of the disease varies from mild forms to life-threatening complications. The mortality of SSc is the highest among rheumatic diseases along with significant morbidity. SSc is divided into different subtypes based on the extent of the skin fibrosis: diffuse cutaneous systemic sclerosis (dcSSc), limited cutaneous systemic sclerosis (lcSSc) and systemic sclerosis sine scleroderma (ssSSc) (Denton et al. 2017; LeRoy et al. 2001).

In dcSSc, all skin areas of the body are affected, whereas in lcSSc skin thickening is limited distal to the elbows and knees. The skin of the face is typically affected in both above-mentioned subtypes. In ssSSc, typical internal organ involvement, combined with SSc-specific autoantibodies or capillary abnormalities, is observed without typical skin involvement (Denton et al. 2017).

Rheumatic or other autoimmune diseases occurring simultaneously is common. In the SSc overlap syndromes, one or more connective tissue diseases (CTD) occur concomitantly. Among other autoimmune diseases, autoimmune thyroiditis and primary biliary cholangitis (PBC) often occur simultaneously with SSc (Elhai et al. 2013).

Globally, the incidence and prevalence of the disease are substantially different. Asia has the lowest rates, whereas North America has the highest rates. The annual incidence rates vary between 0.8 and 4.6 in 100 000 person-years. In Europe, there seems to be an incident gradient from the northern parts to the southern parts, with higher incidence rates in southern Europe (Bairkdar et al. 2021; Zhong et al. 2019). Moreover, the classification criteria applied significantly impact these rates. The reformed American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 criteria detect milder cases, i.e. limited phenotype or the absence of fibrosis, in which autoantibodies and nailfold capillaroscopy have a role. The older ACR 1980-criteria emphasise established fibrosis and damage (van den Hoogen et al. 2013; Masi et al. 1980). SSc is more common in females than males, with the female to male ratio varying between 3:1 and 7–8:1 (Hughes et al. 2020).

SSc has the worst prognosis among rheumatic autoimmune diseases. Cardiopulmonary causes are the most common causes of death currently, since scleroderma renal crisis (SRC) has become rarer after introducing the angiotensin-converting enzyme inhibitors (ACEi) (Elhai et al. 2012; Rubio-Rivas et al. 2014; Steen et al. 2007). Additionally, the treatment is tailored by different organ manifestations. The EULAR updated the treatment recommendations for SSc in 2023 (del Galdo et al. 2025).

The pathogenic mechanisms have been elucidated, allowing for the discovery of more possible treatment targets (Abraham et al. 2025). There are promising results from the CD19-targeting chimeric antigen receptor (CAR) T-cell therapy for the most severe cases, and the treatment seems to be well-tolerated (Auth et al. 2024). Moreover, new cell-based treatments, anti-fibrotic and anti-inflammatory agents are currently under investigation (Siero Santos et al. 2024; Abraham et al. 2025).

Localized scleroderma (LS), i.e. morphea, shares the same features of the skin like SSc. Skin thickening varies, depending on the subtype. It is still considered a distinct disease, and it does not progress to SSc. However, these two diseases can occur simultaneously. LS does not affect the internal organs (Papara et al. 2023; Knobler et al 2024). The incidence rates of morphea vary from 0.4 to 2.7 per 100 000 and an increasing trend has been observed (Peterson et al. 1997). Two peaks occur in the incidence of morphea, one in childhood and another one in middle-age. Morphea is more common in females than males, with a ratio of approximately 4–6:1 (Papara et al. 2023). In addition to the elevated risk of malignancies, especially in the skin, concomitant autoimmune diseases are common (Leitenberger et al. 2009; Abdusalamova et al. 2025; Boozalis et al. 2019).

2 Review of the Literature

2.1 Systemic sclerosis

2.1.1 Pathogenesis

2.1.1.1 The role of vasculopathy and fibrosis

Microvascular abnormalities triggered by an endothelial injury cause vasculopathy, a key feature in the pathogenesis of SSc (Matucci-Cerinic et al. 2013). An endothelial injury leads to the release of multiple cytokines, vascular remodelling, accelerated apoptosis and activation of the immune system. Endothelial apoptosis leads to the release of transforming growth factor β (TGFβ) and connective tissue growth factor (CTGF), leading to fibroblast activation and the accumulation of extracellular matrix (ECM), as well as platelet activation and the release of platelet-derived growth factors. In addition to microvascular disease, macrovascular involvement with the thickening of the arterial wall is frequently observed in SSc. Raynaud′s phenomenon (RP) is typically the first sign of a vascular injury. Figure 1 presents the pathogenesis of SSc.

Vascular permeability increases resulting in oedema in very early SSc. It precedes tissue fibrosis. Essential in promoting vascular health, vascular endothelial-cadherin (VE-cadherin) and Tie2 receptors initiate endothelial junctional signalling. However, this system is disrupted in SSc (Flavahan 2021).

Early studies have revealed the increase in skin solubility and increased synthesis of type I and III procollagens among scleroderma patients (Uitto et al. 1970; Uitto et al. 1979). ECM contains different subtypes of fibroblasts, with variable roles in the pathology of SSc (Abraham et al. 2025). The alterations of T-cells, especially helper T-cells, and B-cells have been found in the circulation of SSc patients. The impairment of the adaptive immune system may be caused by these imbalances (Wu et al. 2024).

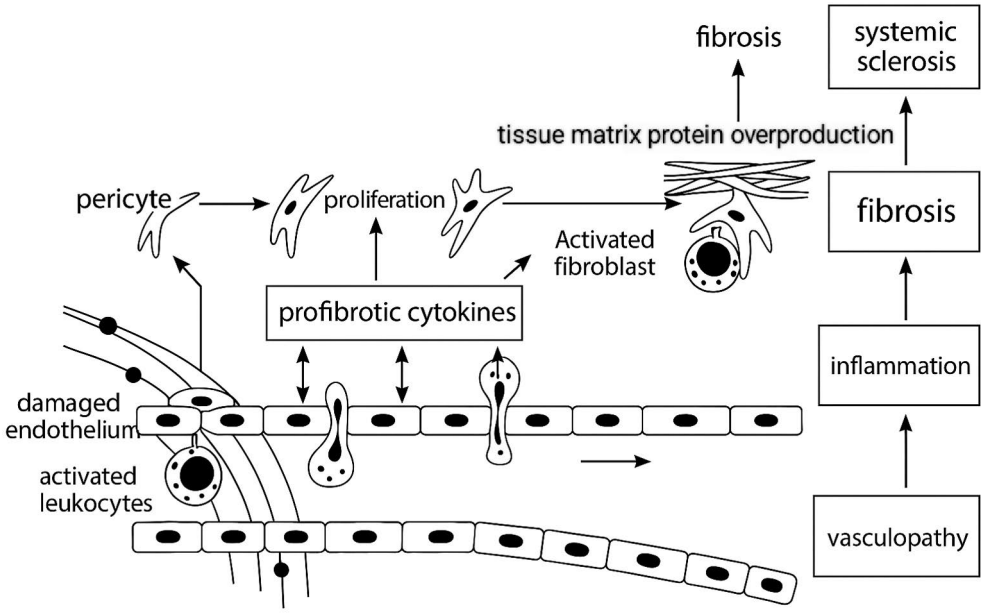

Figure 1. The pathogenesis of systemic sclerosis. The image has been modified from the textbook of rheumatic diseases (Duodecim 2023) using ChatGPT. The original illustration was created by Tiina Ripatti-Toledo, and permission to use the image has been obtained from Duodecim (Kauppi et al. 2023).

2.1.1.2 Genetic factors and immunopathogenesis

SSc is a rare disease with wide variation in its incidence and prevalence worldwide (Bairkdar et al. 2021). It is also observed that family members have an increased risk for the disease. In the study from the US, SSc was more common among first-degree relatives than the general population. The percentages were 1.6% and 0.026%, and the difference was statistically significant (Arnett et al. 2001).

Multiple genes have been identified to be associated with SSc and the clinical features of the disease and distribution of different autoantibodies (Agarwal et al. 2008; Gumkowska et al. 2024). The affecting genes are categorised as follows: Major Histocompatibility Complex (MHC) Region HLA genes, MHC Region non-HLA genes, non-MHC Region genes, genes involved in cytokine synthesis regulation and immune signalling pathway regulation. These genes all have different clinical associations. Interleukin-6 (IL-6), a proinflammatory cytokine, has a role in vascular damage and fibrosis development in SSc. Elevated levels of IL-6 are observed in patients with SSc, especially in those with the dcSSc subtype, elevated CRP and thrombocytosis (Khan et al. 2012). Polymorphism of the IL-6 gene has been associated with different SSc related manifestations and more severe form of

the disease (Gumkowska-Stroka et al. 2024). As a recent European study of 9095 SSc patients identified 13 new gene loci, the total amount of SSc risk loci is now 28 (López-Isac et al. 2019).

The increased expression and activation of type 1 interferon (T1 IFN)- regulated genes has been observed in patients with SSc. Plasmacytoid dendrite cells (pDCs) play an essential role in the T1 IFN activation and the release of cytokines, like chemokine [C-X-C motif] ligand 4 (CXCL4), which is associated with the presence and worsening of SSc-related complications, such as lung fibrosis and pulmonary hypertension. Interferon activation markers may be useful in predicting the severity of the disease and response to the treatment (Kakkar et al. 2022).

2.1.1.3 Environmental factors

In addition to genetic susceptibility, environmental factors such as toxins and viruses have a role in triggering the autoimmune inflammation. Among the autoantibodies, evidence indicates that cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19 may play a role in vascular injuries (Kawaguchi et al. 2023).

Environmental exposures to toxins may have a role in the disease pathogenesis. These factors include silica, solvents, epoxy resins and breast implants (Asano 2020). In an Australian study of 1670 SSc patients, 126 (7.5%) had previous exposure to silica (Patel et al. 2020).

2.1.1.4 Autoantibodies

As SSc is a classic autoimmune disease, different circulating autoantibodies are an important feature of immunological abnormality, playing an important role in the pathogenesis of the disease (Stochmal et al. 2020). Antinuclear antibodies (ANA) are detected in 90–95% of patients with SSc and the proportion of patients with different SSc specific autoantibodies vary, depending on the race and ethnicity (Steen et al. 2005). Three SSc-specific autoantibodies are included in the revised ACR/EULAR 2013 classification criteria (Van den Hoogen et al. 2013). Positivity for ANA is included in the very early diagnosis of SSc (VEDOSS) criteria (Table 1). ANA positivity, Raynaud′s phenomenon (RP) and puffy fingers should lead to a suspicion of very early SSc. For these patients, nailfold videocapillaroscopy (NVC) should be performed and SSc-specific autoantibodies analysed (Avouac et al. 2011). Later, the risk factors for progression to SSc were analysed using the VEDOSS criteria. The impact of each risk factor was analysed individually and in pairs. Patients with puffy fingers and SSc-specific autoantibodies had a 94.1% risk of progressing to SSc within five years. SSc-specific autoantibodies included anticentromere (ACA)-, antitopoisomerase (ATA)- or anti-RNA Polymerase 3

(RNAPol3) antibodies alone or in combination. The effects of these antibodies were not analysed separately (Bellando-Randone et al. 2021).

Table 1. VEDOSS-criteria modified from Bellando-Randone et al. (2021). The 5-year risk of progression to definite systemic sclerosis among patients with Raynaud's phenomenon.

Proportion fulfilling 2013 ACR-EULAR criteria		**ANA**	**SSc-Ab**	**SSc pattern on NVC**	**Puffy fingers**
In the presence of	ANA	58.9%	70.2%	75.0%	79.0%
	SSc-Ab	70.2%	70.2%	82.2%	**94.1%**
	SSc- pattern on NVC	75.0%	82.2%	70.1%	69.2%
	Puffy fingers	79.0%	**94.1%**	69.2%	70.8%
In the absence of	ANA	10.8%	31.0%	40.4%	47.5%
	SSc-Ab	31.0%	31.0%	41.9%	49.6%
	SSc-pattern on NVC	40.4%	41.9%	41.5%	50.9%
	Puffy fingers	47.5%	49.6%	50.9%	47.9%

ANA; antinuclear antibody, NVC; nailfold videocapillaroscopy, SSc; systemic sclerosis, VEDOSS; very early diagnosis of systemic sclerosis,

For detecting antinuclear antibodies, the four main laboratory techniques are available: indirect immunofluorescence (IIF), enzyme-like immunosorbent assay (ELISA), immunodiffusion (ID) and immunoblotting (IB). By assessing the staining pattern of ANA via IIF using human epithelial type 2 (HEp-2) cells, the specific autoantibody is assessable. Table 2, modified from Stochmal et al. (2020), presents different SSc-specific autoantibodies, their prevalence, staining patterns and different clinical associations.

The different SSc-specific autoantibodies are associated with different disease-related manifestations, disease subtypes and prognosis, all of which show varying frequencies (Kuwana 2017). Proposed by LeRoy et al. (1988) SSc is commonly divided into subgroups by skin involvement. ATA, also named Scl-70-antibodies, are strongly linked to dcSSc, interstitial lung disease (ILD) and primary heart involvement (pHI). ACA are associated with lcSSc, and those patients had more calcinosis of skin and soft tissues and telangiectasias (Steen et al. 1988). Vasculopathy leading to digital ulcers (DUs) and pulmonary arterial hypertension (PAH) is associated with ACA positivity in SSc patients (Steen et al. 2005). According to Gelber et al. (2006), ACA are also frequently detected in other conditions, such as Sjögren′s disease (SjD). In their study, 10 out of 45 (22%) of SjD patients were ACA-positive. However, patients with SjD recognise only CENP-C, while patients with SSc recognise both CENP-B and CENP-C. Less common SSc-

specific autoantibodies and their frequencies are presented in Table 2. Out of all these autoantibodies, anti-RNAPol3 is the most common of and it is included in the ACR/EULAR 2013 classification criteria.

Autoantibodies combined with the cutaneous classification can also be used in assessing the prognosis and different disease-related complications. In a single centre study, the worst prognosis was in dcSSc patients with ATA antibodies. Notably, patients with anti-U3 RNP-antibodies had a similar 5-year mortality rate with 14.6%, while the 20-year mortality rates differed: 67.6% for ATA-positive patients versus 39.5% for anti-U3 RNP-positive patients, respectively. Anti-U3 RNP-positive patients had high mortality early in the disease course. The patients with lcSSc with ACA had the best prognosis with a 65.3% 20-year survival rate. Anti-RNAPol3 antibodies were associated with a high risk of scleroderma renal crisis (SRC); 23% of patients developed SRC during the first five years of the disease. Meanwhile, the risk of clinically significant pulmonary fibrosis was less than half of those with ATA-positive patients. These percentages were 34% and 80%, respectively, during the first five years of the disease (Nihtyanova et al. 2020). Anti-RNAPol3 antibody-positive SSc patients showed an increased risk of cancer compared to ACA- or ATA-positive SSc patients; the percentages of these risks were 14.2%, 6.8% and 6.3%, respectively, with the most commonly detected malignancy being breast cancer (Moinzadeh et al. 2014). In contrast, an increased risk of cancer was observed among ATA-positive patients in another study, with an overall 1.4-fold increased risk (Mahajan et al. 2025).

In a large study of the prospective European Scleroderma Trials and Research Group (EUSTAR) cohort, stratification by SSc-specific autoantibodies predicted better overall survival, disease progression and different organ damage than stratification by cutaneous subtype. In this study, in addition to ANA, only three main SSc specific autoantibodies were analysed: ACA, ATA and anti-RNAPol3. ANA was positive for 95.2% of patients. The percentages of isolated ANA -, ACA -, ATA - and anti-RNAPol3 positivity were as follows: 28.1%, 36.4%, 27.6% and 3.1%. Patients with ACA had the highest overall survival rate and progression-free survival rate. Additionally, patients with ATA had the lowest progression-free survival rate, while autoantibody-negative patients had the lowest overall survival rate and worst prognosis (Elhai et al. 2022)

Table 2. Different systemic sclerosis related autoantibodies, their frequencies and clinical associations. Modified from Stochmal et al. (2020).

Antinuclear antibodies	Prevalence	SSc subtype	Staining pattern	Organ involvement and associated diseases
Anti-TOPO I (ATA, Scl-70)	9.4–42%	Diffuse	Speckled	ILD, SRC, digital ulcers early in the disease
Anticentromere (ACA)	20–40%	Limited	Discrete speckled	PAH, digital ulcers late in the disease
Anti-RNA polymerase III	11%	Diffuse	Speckled (+/- nucleolar)	Higher risk of malignancy, SRC, gastric antral vascular ectasia
Anti-U3 RNP (anti-fibrillarin)	4–10%	Diffuse/limited	Nucleolar	ILD, PH, SRC, myocardial fibrosis, GI-involvement, myositis
Anti-U1 RNP	6–7%	Limited	Speckled	MCTD, arthritis, myositis
Anti Th/To	2–5%	Limited	Nucleolar	ILD, PH, myositis
Anti-NOR 90/hUBF	4.8%	Limited	Nucleolar	Rheumatoid arthritis, Sjögren's disease
Anti-U11/U12 RNP	3%	Diffuse/limited	Speckled	ILD, PH
Anti-PM/Scl	2%	Limited	Nucleolar	Myositis overlap
Anti-Ku	1.5–5%	Limited	Speckled	Myositis, arthritis
Anti-RuvBLl/2	1–2%	Diffuse	Speckled	Myositis
Anti-eIF 2B	1%	Diffuse	Speckled cytoplasmic	ILD

GI; gastrointestinal, ILD; interstitial lung disease, MCTD; mixed connective tissue disease, PAH; pulmonary arterial hypertension, PH; pulmonary hypertension, SRC; scleroderma renal crisis, SSc; systemic sclerosis.

In addition to SSc-specific autoantibodies, anti-SSA antibodies (TRIM21, Ro52) are frequently detected in SSc patients (Martel et al. 2024; Watanabe et al. 2024). Overlapping with SjD is frequent, although these antibodies are also detected solely in SSc patients. In the study by Martel et al, with a French cohort, systematic review and meta-analysis, the prevalence of anti-SSA antibodies was 26% and associated with the female gender, lcSSc, joint manifestations, pulmonary hypertension (PH) and ILD. In a Japanese single centre cohort study, anti-SSA-antibody positivity was associated with ILD and more severe skin fibrosis (Watanabe et al. 2024). Chan (2022) also showed SSA-antibody association with more severe ILD in CTDs.

ANA negativity is rare in SSc. In a study from the US, 208 (6.4%) of 3249 SSc patients were negative for ANA. These patients had less complications related to vasculopathy but more severe gastrointestinal (GI) involvement. No difference was

observed in the overall survival or occurrence of pulmonary fibrosis or SRC (Salazar et al. 2015).

2.1.2 Diagnosis

2.1.2.1 Classification criteria

The classification criteria applied play a significant role in diagnosing SSc. However, the diagnosis can be made without fulfilling all the criteria listed.

The main purpose of the preliminary criteria, established in 1980 by the American Rheumatism Association (Masi et al. 1980), was to distinguish SSc from other CTDs. They were designed to be specific rather than sensitive to prevent false positive diagnoses. Later, in order to obtain better sensitivity, criteria for early SSc were proposed (LeRoy et al. 2001), which included NVC abnormalities and SSc-specific autoantibodies. The ACR/EULAR 2013 criteria were proposed to obtain even better sensitivity. In these criteria, NVC and SSc-specific autoantibodies have a significant role. Thus, the criteria could be fulfilled without any thickening of the skin, as they also detect sine scleroderma (ssSSc) cases. The sensitivity and specificity of the latest criteria are 0.91 and 0.92, respectively, versus 0.75 and 0.72 for the oldest criteria. Table 3 presents the details of these criteria.

In the early SSc criteria by LeRoy and Medsger, the SSc selective autoantibodies were as follows: ACA, ATA, anti-fibrillarin, anti-PM-Scl, anti-fibrillin and anti-RNA polymerase I or III in a titre of 1:100 or higher.

Table 3. Classification criteria for systemic sclerosis

Criteria	Characteristics
ACR 1980 criteria	**Major criteria:** • Proximal cutaneous sclerosis/skin thickening (non-pitting) proximal to MCPs **Minor criteria:** • Sclerodactyly • Digital pitting scars of fingertips or loss of substance of the distal finger pad • Bibasalar pulmonary fibrosis **Requirement for diagnosis:** One major or two or more minor criteria
LeRoy and Medsger 2001 criteria for early SSc	**Limited SSc (lSSc):** • Raynaud′s phenomenon (objective documentation) plus SSc-type nailfold capillary pattern or SSc selective autoantibodies or • Raynaud′s phenomenon (subjective only) plus SSc-type nailfold capillary pattern and SSc selective autoantibodies **Limited cutaneous SSc (lcSSc):** • Criteria for lSSc plus distal cutaneous changes **Diffuse cutaneous SSc (dcSSc):** • Criteria for lSSc plus proximal cutaneous changes **Diffuse fasciitis with eosinophilia (DFE):** • Proximal cutaneous changes without criteria for lSSc or lcSSc
ACR/EULAR 2013 criteria	**Proximal skin involvement** • Skin thickening of the fingers of both hands, extending proximal to the metacarpophalangeal joints (sufficient criterion; score 9) **Skin thickening of the fingers (only count the higher score)** • Puffy fingers (score 2) • Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints; score 4) **Fingertip lesions (only count the higher score)** • Digital tip ulcers (score 2) • Fingertip pitting scars (score 3) **Telangiectasia (score 2)** **Abnormal nailfold capillaries (score 2)** **Pulmonary arterial hypertension or interstitial lung disease (maximum score 2)** • Pulmonary arterial hypertension (score 2) • Interstitial lung disease (score 2) **Raynaud′s phenomenon (score 3)** **Systemic sclerosis-related autoantibodies (maximum score 3)** • Anti-centromere (score 3) • Anti-topoisomerase I (score 3) • Anti-RNA polymerase III (score 3) **Requirement for diagnosis:** A total score of 9 or more

ACR; American College of Rheumatology, EULAR; European League Against Rheumatism, MCP; metacarpophalangeal, SSc; systemic sclerosis

2.1.2.2 Nailfold videocapillaroscopy

As nailfold capillaroscopic abnormalities are detected in over 90% of SSc patients, they are included in the revised classification criteria (van den Hoogen et al. 2013). NVC has an essential role in distinguishing primary RP from secondary causes.

The digital videocapillaroscope with 200x magnification is the gold standard device and abnormalities can be divided into a scleroderma pattern and non-specific abnormalities (Smith et al. 2020). NVC is performed in the nailfolds of four fingers in the hands, excluding the thumbs. Four pictures per finger are taken and the parameters analysed are as follows: capillary density, dimension, morphology and microhaemorrhages (Smith et al. 2023). Normal capillary density is from 7 to 12 capillaries per linear millimetre. The dimension of the capillary is measured in the apex of the capillary loop. A normal capillary diameter is 20 micrometres or below. Giant capillaries are enlarged, over 50 micrometres in the apical diameter. Normal morphology is considered a normal "hairpin" shape or tortuous shape, while others like ramifications, neo-angiogenesis and meandering shapes are considered abnormal. A fast track algorithm was established by Smith et al. (2019) to differentiate scleroderma pattern from non-scleroderma pattern, which include a variety of nonspecific abnormalities. If the capillary density is 7 or more capillaries per millimetres and no giant capillaries are detected, scleroderma pattern is not observed.

Cutolo et al. (2000) graded SSc microangiopathy by NVC into three patterns: early, active and late. In the early pattern, capillary density is normal and giant capillaries are present. In the active pattern, density is decreased and giant capillaries are present. In the late pattern, density is decreased, morphology is abnormal and no giant capillaries are detected. Microhaemorrhages are frequently observed in the active pattern, rarely seen in the early pattern and absent in the late pattern. In combining the NVC pattern and different autoantibodies, the presence of ATA was associated with an earlier expression of active and late patterns, and the presence of ACA was associated with a delayed expression of the late pattern (Cutolo et al. 2004). A similar finding was observed in a study by Sulli et al. (2020). Figure 2 presents early and active NVC patterns.

A semiquantitative rating score was developed to score microangiopathy in SSc. The extent of microvascular abnormalities was rated from 0 to 3 (0=no changes, 1= <33% capillary alterations/reduction per linear millimetre, 2= 33–66% capillary alterations/reduction per linear millimetre, 3= >66% capillary alterations/reduction per linear millimetre). The parameters were the loss of capillaries, disorganisation of the microvascular array and capillary ramifications. Giant capillaries were not included in this score, since they present early stages of the microangiopathy. This score is useful in determining the evolution of microvascular damage (Sulli et al. 2008). In an Italian study analysing the progression of NVC, higher NVC scores

were associated with organ involvement. In the same study, organ involvement was found more frequently in those who progressed from an early pattern to an active or late NVC pattern. In comparing late and active patterns, organ involvement was more frequent in the late pattern than the active NVC group (Sulli et al. 2012).

Advanced NVC changes (active and late) are also associated with more severe organ involvement in other studies (Smith et al. 2013; Vanhaecke et al. 2022; Tolosa-Vilella et al. 2023) and with reduced survival in dcSSc patients due to SSc-related causes (Tolosa-Vilella et al. 2023). On the other hand, normal or non-specific NVC is associated with less severe skin involvement and less frequent severe pulmonary involvement (Fichel et al. 2014).

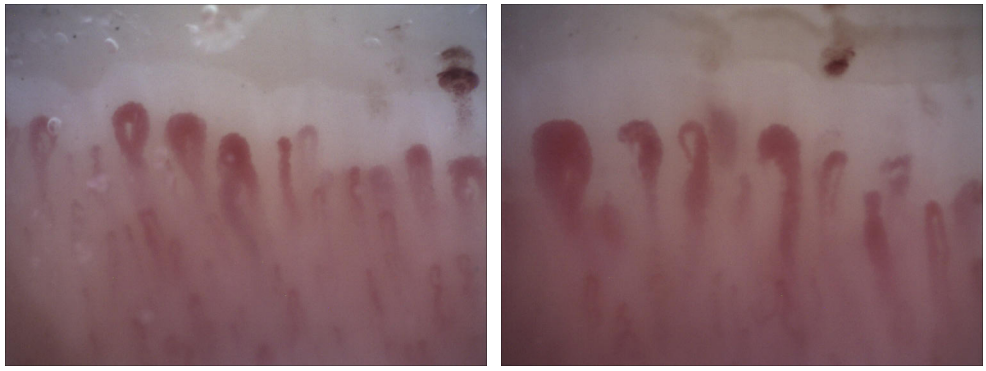

Figure 2. Nailfold videocapillaroscopy (NVC) findings. Pictures are taken at the same session from the same patient with limited cutaneous systemic sclerosis (lcSSc). On the left picture is an early SSc pattern where density is normal but giant capillaries are observed. On the right is an active SSc pattern where density is decreased and giant capillaries are still present. Permission to present the images was obtained from the patient.

2.1.2.3 Imaging and other diagnostic methods

As the diagnostic criteria of SSc are lacking, the clinical evaluation, using the classification criteria combined with NVC and autoantibodies, is essential in making the diagnosis. In addition, many imaging and other diagnostic methods are needed. After making the diagnosis, these methods are needed in screening and following many organ involvements in SSc patients, all of which are discussed later in its own chapter.

The most commonly used imaging modalities are x-ray, ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) scans. An X-ray of the hands can reveal calcinosis, acro-osteolysis of fingertips, and soft tissue thinning, but sometimes it is needed in the differential diagnosis. A thoracic x-ray can reveal larger changes of ILD, and it is sometimes useful in the follow-up due to

the smaller exposure to radiation. A video fluorography swallow study can be used to evaluate oesophageal motility (Rutka et al. 2021). US is used in assessing the skin, musculoskeletal system, lungs, cardiovascular system and kidneys. In addition to echocardiography, right heart catheterisation is needed in diagnosing PAH. Echocardiography is a useful method to assess diastolic heart insufficiency due to myocardial fibrosis and the extent of atherosclerosis (Rutka et al. 2021). High resolution computed tomography (HRCT) is mandatory in SSc patients in screening for ILD (Hoffmann-Vold et al. 2020). CT visualises abnormalities in the esophagus in SSc patients. MRI is a useful modality to assess the morphology of the heart, and it can reveal cardiac fibrosis due to primary heart involvement; it is also a method used to evaluate the musculoskeletal system. It can show abnormalities in the skin and gastrointestinal (GI) tract as well (Rutka et al. 2021).

Pulmonary function tests (PFTs), spirometry and diffusion capacity of the lung for carbon monoxide (DLCO) are used in screening and following patients with SSc (Hoffmann-Vold et al. 2020). An isolated decline in DLCO can be a sign of PAH. A 6-minute walking test is used at the diagnosis and during the follow-up in patients with PAH or ILD.

An upper endoscopy and sometimes a manometry are needed to evaluate the symptoms of the upper GI tract. Along with imaging methods, sometimes, e.g. colonoscopy, intestinal manometries, scintigraphy and capsule techniques, are needed to evaluate the lower GI tract involvement (Volkmann et al. 2022). The extent of skin fibrosis can be assessed clinically using a modified Rodnan Skin Score (mRSS) (Khanna et al. 2017). When assessing the disease activity, the patient reported outcomes (PROs) play a role in it.

2.1.2.4 Differential diagnosis

Not only is RP typically the first symptom of incipient SSc, but it is also a common symptom, affecting approximately 5% of people (Herrick et al. 2020). It is important to distinguish benign primary RP from secondary RP in which the underlying cause might be CTD like SSc. Autoantibodies, NVC and clinical parameters, like puffy fingers and severe ischaemic attacks, should lead to a suspicion of SSc. In primary RP, up to 50% of patients have first-degree relatives with RP.

Thickening of the skin is a nonspecific manifestation, which can be caused by several conditions. The absence of RP, autoantibodies and nailfold capillaroscopic changes should lead to a suspicion of other diseases and a skin biopsy is often required.

In a review by Tyndall et al. (2013), the different SSc mimickers are represented, which are divided into local and diffuse mimics. Local mimics include morphea and stiff skin syndrome, and diffuse mimics are presented in Table 4.

Table 4. Diffuse mimics of systemic sclerosis modified from Tyndall et al. 2013.

Inflammatory and immune-mediated disorders	Overlap CTDs	Deposition disorders	Metabolic conditions	Toxic agents	Genetic diseases
Eosinophilic fasciitis Graft versus host disease	Overlap CTD Paraneoplastic phenomenon	Scleromyxodema Scleroedema adultorum Amyloidosis Nephrogenic systemic fibrosis	Phenylketonuria Porphyria cutanea tarda Hypothyroidism	Silica Polyvinyl chloride Bleomycin Toxic oil syndrome	Progeria Werner's syndrome

CTD; connective tissue disease

Several of these conditions are rare or they are obvious by clinical picture. Morphea is limited to the skin, but it rarely affects the skin widely. Disabling pansclerotic morphea is a severe form of the disease, although it does not affect internal organs.

Eosinophilic fasciitis is the most common diffuse mimicker. Typically, skin is affected in the deep layers and a biopsy including deep fascia and muscle is recommended to perform, guided by MRI.

Scleromyxoedema, a very rare condition, represents many similarities like SSc. The skin of the face with a limited mouth opening and sclerodactyly are present and internal organ manifestations are seen. However, vasculopathy is not a feature. Scleromyxoedema is almost always associated with IgGλ gammapathy.

Scleroedema adultorum is often seen in children and is associated with either acute respiratory infection, paraprotein or insulin-dependent diabetes mellitus. Typically, the skin is thickened in the back, neck and shoulder girdle.

Nephrogenic systemic fibrosis is seen in patients with chronic kidney failure after exposure to gadolinium. In addition to the skin, internal organs are typically affected.

In order to select an accurate treatment, it is essential to rule out these SSc mimics in clinical practice.

2.1.3 Epidemiology

2.1.3.1 General aspects

SSc is a rare disease with wide geographical differences in its prevalence and incidence. It is challenging to compare the studies, as both the methods and

classification criteria vary. As the latest ACR/EULAR 2013 criteria (Van Den Hoogen et al. 2013) detect milder cases without skin fibrosis, an increasing trend in the incidence has been observed in the latest studies. While some studies have used the older criteria, there are studies conducted by using ICD codes or a doctor′s opinion for the basis of the diagnoses. Two systematic reviews and meta-analyses present the prevalence and incidence rates worldwide and the methodology used in different studies (Zhong et al. 2019; Bairkdar et al. 2021). The data are lacking from some parts of the world, e.g. Africa. The African American ethnicity is a known risk factor for more severe diseases. SSc is more common among females than males, with a female to male ratio varying between 3:1 and 7–8:1 (Hughes et al. 2020). Meanwhile, males tend to have a more severe disease.

2.1.3.2 Geographical differences

The incidence rates of SSc varies worldwide, the rates of which are the lowest in Asia, with estimated annual incidence rates of 0.8–1.1 per 100 000 inhabitants (Kang et al. 2018; Kuo et al. 2011). Conversely, the highest rates are found in North America. During the years 2003 through 2008 in the United States, the estimated incidence was 4.6 per 100 000 inhabitants (Furst et al. 2012). In other studies from North America, the annual incidence rates varied from 1.4 to 16.4 per 100 000 inhabitants (Fan et al. 2020; Mayes et al. 2003; Steen et al. 1997). According to the findings by Steen et al., the annual incidence in the United States increased during the years 1963 through 1982, from 9.7 per million inhabitants to 18.2 per million inhabitants.

There is an incidence gradient in Europe from the northern parts to the southern parts, with higher incidence rates in Southern Europe. In studies from North Italy during the years 1999 through 2007 (LoMonaco et al. 2011) and Spain during the years 1988 through 2006 (Arias-Nunez et al. 2008), the annual incidence rates were 3.2 and 1.2 per 100 000 with the utilisation of the ACR 1980-criteria, and 2.3 and 4.3 with the utilisation of the LeRoy-Medsger criteria. According to some older studies from Northern Europe, the incidence varied from 0.4–0.8 per 100 000 inhabitants (Geirsson et al. 1994; Silman et al. 1988; Kaipiainen-Seppänen et al. 1996; Vonk et al. 2009). A Swedish register study showed a higher incidence than previously reported in Northern Europe (Andreasson et al. 2014). Between 2006 and 2010, the mean annual incidence was 1.4 per 100 000 inhabitants with the utilisation of the ACR 1980-criteria and 1.9 per 100 000 with the utilisation of the ACR/EULAR 2013 criteria.

The overall prevalence has been reported to range from 17.6 to 23 per 100 000 inhabitants (Bairkdar et al. 2021; Zhong et al. 2019).

2.1.4 Clinical manifestations and organ-based treatments

2.1.4.1 Subtypes of systemic sclerosis

The distinction between SSc patients is made by evaluating the extent of skin fibrosis (LeRoy et al. 1988). The subtypes of SSc are dcSSc, lcSSc and ssSSc. In dcSSc, skin is affected proximally on the body, including the trunk, upper arms and thighs. In lcSSc skin, thickening is limited distal to elbows and knees. The skin of the face is typically affected in both above-mentioned subtypes (Figure 3). In ssSSc, typical internal organ involvement, combined with SSc-specific autoantibodies or capillary abnormalities, is observed without any thickening of the skin.

Defining ssSSc is sometimes challenging because internal organ manifestations can precede skin thickening. Kucharz et al. (2017) proposed the classification of ssSSc into three groups: Type I (complete) is defined as the lack of any skin changes typical for SSc. In type II, no thickening of the skin or sclerodactyly is observed but other findings, like calcifications, telangiectasias and pitting scars, can be found. In type III, skin changes are delayed. In a Canadian study of 1417 patients with SSc, only 57 were considered to have ssSSc. Of those, 30 patients were later reclassified as having lcSSc. Only 27 patients (1.9%) were classified as having ssSSc. The clinical feature of ssSSc was similar or milder than lcSSc, with a similar occurrence of ILD or PAH but a lower frequency of DUs or pitting scars. Overall, ssSSc was a milder disease than dcSSc. The occurrence of an overlap disease was very rare in ssSSc patients. Serological features were similar to lcSSc patients with high rates (50%) of ACA positivity (Diab et al. 2014). In a Spanish study of 45 ssSSc and 186 lcSSc patients, no difference was seen in internal organ involvement or survival between the groups. The prevalence of ANA, ACA and NVC patterns was also similar. However, ssSSc patients had sicca syndrome, DUs and calcinosis less frequently (Simeon-Aznar et al. 2014).

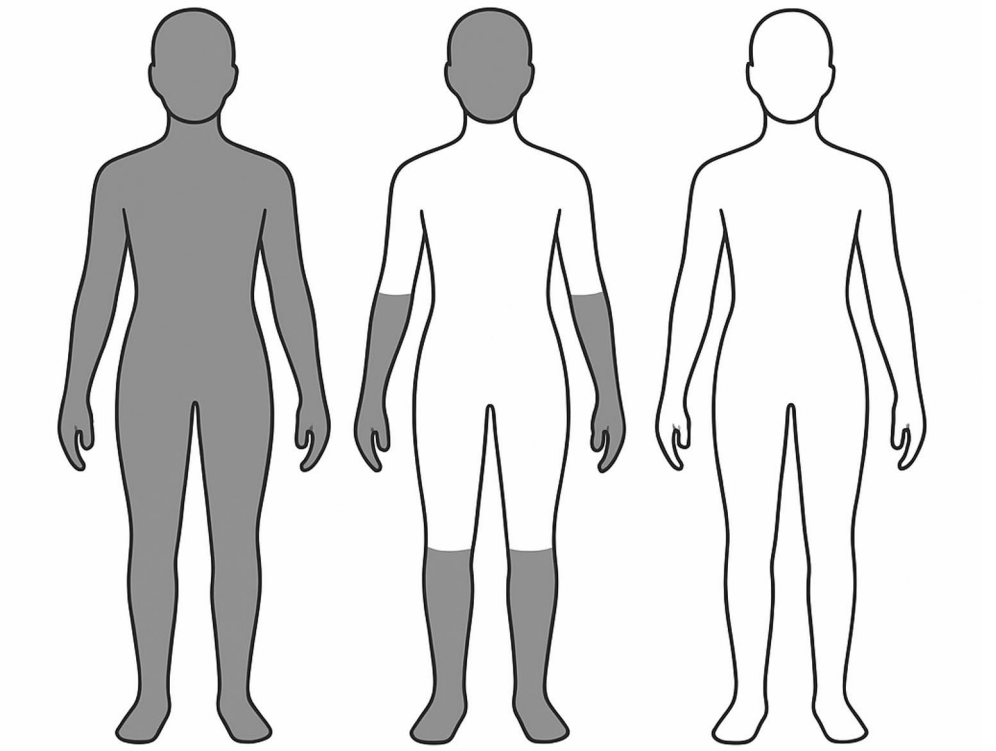

Figure 3. The distribution of affected skin areas in different systemic sclerosis (SSc) subtypes. The figure on the left presents diffuse cutaneous (dcSSc) subtype, the figure in the middle limited cutaneous (lcSSc) subtype, and the figure on the right, sine scleroderma (ssSSc) subtype. Created with ChatGPT.

In a recent study conducted with the utilisation of the EUSTAR database encompassing 4263 SSc patients, ssSSc was detected in 376 (8.8%) of patients. The frequency of ILD was almost 50%, similar to lcSSc but less common than dcSSc (75%). The frequency of puffy fingers and DUs was lower than in other subtypes and survival was better. Interestingly, the frequency of SRC was 3% in the ssSSc subtype (Lescoat et al. 2023).

2.1.4.2 Interstitial lung disease

ILD is a common fibrotic manifestation in SSc (Joy et al. 2023; Perelas et al. 2020) affecting 47–84% of patients with SSc (Distler et al. 2020). It is also a leading cause of death in SSc (Elhai et al. 2012), autopsies have revealed up to a 90% prevalence of ILD, though 30-40% develop a clinically significant disease and it typically occurs at the early stage of the disease. In the pathogenesis, injury in both the vascular endothelial and alveolar epithelial cells is the initial event. Fibroblast activation leads

to fibrosis in the interstitium and scarring of the lungs (Perelas et al. 2020). Gastroesophageal reflux disease (GERD) is one potential trigger for a lung injury (Christmann et al. 2010). The most common ILD pattern on a chest CT is nonspecific interstitial pneumonia (NSIP), and usual interstitial pneumonia (UIP) is found in a minority of the patients (Joy et al. 2023). While a lung biopsy or bronchoalveolar lavage (BAL) are not routinely performed in SSc-ILD patients, they are sometimes useful in the differential diagnosis (Khanna et al. 2020). Due to the high prevalence of ILD among SSc patients, HRCT should be performed routinely for all new SSc patients and pulmonary function tests (PFTs) should be performed regularly (Hoffmann-Vold et al. 2020). The latest European Respiratory Society (ERS)/EULAR guidelines recommend a 3-to-12-month frequency regarding PFTs, depending on the risk factors and the duration of the disease. These recommendations also suggest considering an annual HRCT screening for the patients with the highest risk (Antoniou et al. 2025).

Several risk factors for the development and progression of ILD have been identified. The most important risk factors for the development of SSc-ILD include age, male gender, African American ethnicity and the dcSSc subtype. Autoantibodies, like ATA and SSA-antibody positivity and several biomarkers, are risk factors for SSc-ILD. (Perelas et al. 2020; Khanna et al 2020).

Moreover, there are different definitions for the progression of ILD. The factors include respiratory symptoms, radiological progression and physiological progression by PFTs. In clinical practice it is important to identify patients in the risk of progression as the majority of them have a stable or indolent disease. The known epidemiological risk factors for progression include the male gender, smoking and older age. There are several disease-related risk factors, including DUs and progressive skin fibrosis. Decreased pulmonary function tests and a larger extent of fibrosis on HRCT, UIP pattern and biomarkers, such as high CRP, are also known risk factors (Perelas et al. 2020; Distler et al. 2020). In a study utilising the EUSTAR database of 826 patients with SSc-ILD, 27% experienced ILD progression during the first 12 months. During the subsequent five-year period, 23–27% progressed (Hoffmann-Vold et al. 2021).

Non-pharmacological treatments of SSc-ILD include lifestyle interventions such as smoking and nicotine product cessation, vaccines (COVID, influenza and pneumococcal disease), oxygen supplementation and lung transplantation in advanced cases. The treatment of gastroesophageal reflux (GER) with proton pump inhibitors (PPI) is recommended. The updated EULAR recommendations for the treatment of SSc, as well as the ERS/EULAR and ACR/ American College of Chest Physicians (CHEST) guidelines for the treatment of ILD in people with systemic autoimmune rheumatic diseases, were published recently (Del Galdo et al. 2025; Johnson et al. 2024; Antoniou et al. 2025). Pharmacological treatments of SSc-ILD

comprise conventional immunomodulatory drugs, biologics, antifibrotic treatments or their combinations. No preventive effect through the initiation of early immunosuppression for the development of ILD was observed in the study conducted with the utilisation of the EUSTAR database (Velauthapillai et al. 2024).

The first randomised placebo-controlled trial (RCT) was Scleroderma Lung Study I (SLS-I). Treatment with cyclophosphamide (CYC) for 12 months was superior to the placebo in maintaining the lung function (Tashkin et al. 2006). Later, in Scleroderma Lung Study II (SLS-II), Mycophenolate Mofetil (MMF) was found to be equal in efficacy but with less adverse effects (Tashkin et al. 2016).

Out of all the biologics, tocilizumab (TCZ) and rituximab (RTX) both show efficacy in SSc-ILD. An elevated concentration of IL-6 was observed among patients with dcSSc (Khan et al. 2012). By blocking the IL-6 receptor with TCZ, stabilisation of lung function was observed in the phase 2 (faSScinate) and 3 (focuSSced) trials of early inflammatory SSc patients (Khanna et al. 2016; Khanna et al. 2020). The preservation of lung function was later observed despite the extent of ILD or fibrosis in HRCT (Roofeh et al. 2021). When the focuSSced trial data was combined with the single-centre data by Nihtyanova et al. (2020), it was observed that the male sex, disease duration <2 years, age under 65 years, IL-6 levels <10 pg/mL and ATA positivity predicted better a response to TCZ (Ghuman et al. 2024).

RTX, a chimeric antibody against CD20, causes the B-cell depletion of peripheral B cells. In a meta-analysis encompassing 20 studies on SSc-ILD, RTX significantly improved FVC at the 6- and 12-month endpoints and the risk of infections was even lower compared to the placebo group. The studies in this meta-analysis were conducted prior to 2020 (Goswami et al. 2021). In the placebo-controlled study with RTX (DESIRES), in which the effect of skin fibrosis was the primary endpoint, the lung function improved significantly in the RTX group at week 24 (Ebata et al. 2021). Further, in the 24-week open-label period with RTX, the lung function also recovered in the initial placebo group (Ebata et al. 2022). There was no difference in the occurrence of side effects. RTX also showed a good safety profile in the study conducted with the EUSTAR database of 254 patients treated with RTX, where no improvement of lung function was observed compared to the placebo. Patients concomitantly receiving MMF and RTX showed improvement in lung fibrosis (Elhai et al. 2019). The efficacy of the combination of RTX and MMF versus MMF alone for patients with ILD with a NSIP pattern was observed in the EVER-ILD study (Mankikian et al. 2023). In a RECITAL study consisting of CTD-ILD patients, RTX and cyclophosphamide demonstrated similar efficacy, though fewer side effects occurred in the RTX group (Maher et al. 2023).

In a British single-centre study both RTX and TCZ stabilised lung function in all subgroups of SSc patients. The male gender and ATA positivity predicted better treatment responses in both groups, with the latter being statistically significant in

the TCZ group. ATA-positive patients particularly benefitted from a combination of TCZ and MMF (Goldman et al. 2025). The comparison of effectiveness of TCZ, RTX, MMF and CYC with real-life data from the EUSTAR was conducted recently. The effect on SSc-ILD was comparable between the groups, though CYC was the most effective in the group of immunosuppressant naïve patients (Yan et al. 2025).

Among the mainly anti-inflammatory agents, the antifibrotic drug nintedanib has been approved for the treatment of SSc-ILD. It is a tyrosine kinase inhibitor with antifibrotic and anti-inflammatory effects. The SENSCIS trial showed that nintedanib significantly reduced the decline in the lung function in SSc-ILD patients at 52 weeks. The rates of decline in FVC were -52.4 ml and -93.3 ml in the nintedanib and placebo groups, respectively (Distler et al. 2019). The effect was greater with a concomitant MMF treatment: In the nintedanib group the FCV decline rates were -40.2 ml and -63.9 ml for patients receiving MMF at the baseline or not, respectively. These rates were -66.5 ml and -119.3 ml in the placebo group. The most common adverse effects of nintedanib were gastrointestinal, diarrhoea and nausea (Highland et al. 2021).

In the severe forms of SSc, including SSc-ILD, autologous hematopoietic stem-cell transplantation (HSCT) may be an option. The patient selection is crucial, however; it should be performed early in the disease course with dcSSc patients with poor prognostic markers but without any advanced organ damage. The ASSIST study compared HSCT to intravenous CYC, and HSCT was more effective in improving skin and lung function (Burt et al. 2011). The ASTIS study comparing HSCT and CYC showed better long-time, event-free and overall survival in the HSCT group, although there was 10% treatment-related mortality in the HSCT group in the first year (van Laar et al. 2014). In a systematic review encompassing 38 studies, HSCT slightly improved lung function. Treatment-related mortality was 8.3% and there was a decreasing trend in the latest studies (Eyraud et al. 2018). In a study comprising 80 patients with severe SSc, treatment-related mortality was 6.25%. The treatment regimen was tailored according to patients′ condition. The progression-free survival was 81.8% at two years (Henes et al. 2021).

According to the updated EULAR and ERS/EULAR recommendations RTX, MMF, CYC, TCZ and nintedanib should be considered for the treatment of SSc-ILD. Nintedanib is recommended to be used alone or in combination with MMF (del Galdo et al. 2025; Antoniou et al. 2025). In the ACR/CHEST recommendations regarding CTD-ILD, azathioprine (AZA) could also be an option in the treatment of SSc-ILD (Johnson et al. 2024). HSCT should be considered in the refractory cases and there is a strong recommendation against glucocorticoids, due to the risk of SRC.

2.1.4.3 Skin and musculoskeletal involvement

The thickening of the skin is a striking feature of SSc and its extent varies among different subtypes of SSc. The diffuse cutaneous involvement is associated with a more severe disease and higher prevalence of SSc-ILD (Khanna et al. 2020; Perelas et al. 2020), as well as SRC. Severe organ involvement typically occurs at the early stage of the disease, and these patients have a reduced survival rate (Steen et al. 2000). The higher skin thickness progression rate is associated with reduced survival and a higher incidence of SRC (Domsic et al. 2011).

The most commonly used method to assess skin thickness is mRSS (Khanna et al. 2017). Performing the mRSS requires training and it is dependent on the physician. The areas assessed are: fingers (proximal to the proximal interphalangeal joint), hands, forearms, upper arms, face, anterior chest, abdomen, thighs, legs and feet. The scores are graded from 0 to 3; mRSS 0 is normal skin with fine wrinkles and no skin thickness, mRSS 1 is when there is mild thickness but skin folds are easy to make, mRSS 2 is moderate skin thickness, there are no wrinkles and skin folds are difficult to make, and mRSS 3 is defined as severe skin thickness and skin folds are impossible to make. A maximum score is 51. In dcSSc, the skin thickness typically increases in the first years, and some regression can be observed spontaneously.

The most effective treatment of skin thickness is HSCT (Pope et al. 2023), with its efficacy proven in multiple studies (Eyraud et al. 2018). The use of HSCT is limited to the most severe cases as the treatment-related mortality is high, 10% in the first year (van Laar et al. 2014). Sustained improvement of skin thickness and the stabilisation of organ function have been observed to last up to seven years after the procedure (Vonk et al. 2008). The decline in mRSS was detected in SLS-I for CYC (Tashkin et al. 2006), with a recent meta-analysis of 20 articles indicating similar results (Tian et al. 2025). CYC and MMF showed efficacy in mRSS on SLS-II for the majority of patients (Tashkin et al. 2016). MMF was beneficial, decreasing mRSS in a study of 98 SSc patients (Le et al. 2011). Methotrexate (MTX) has been beneficial in some studies (Pope et al. 2001; Pope et al. 2023), which is usually prescribed as the first-line treatment as an alternative to MMF.

RTX shows the strongest evidence on efficacy in skin fibrosis among biologics (Elhai et al. 2019; Goswami et al. 2021; Ebata et al. 2021; Ebata et al. 2022). For TCZ, the trend of decreasing mRSS was observed in the focuSSced trial (Khanna et al. 2020), though the difference was not statistically significant. In the SENSCIS-trial, no improvement was observed for skin with nintedanib (Distler et al. 2019).

The musculoskeletal involvement of SSc includes arthritis and myositis, both of which can be sometimes associated with overlap syndrome. Tendon friction rubs can also be present. In the updated EULAR recommendations (del Galdo et al. 2025), MTX should be considered for musculoskeletal involvement. While glucocorticoids

can be beneficial, caution should be exercised as they might trigger SRC. Intravenous immunoglobulin (IVIG) could also benefit some patients. In a Spanish multi-centre retrospective study, IVIG had the greatest impact on inflammatory myositis associated with SSc, and the benefit was also detected in skin and GI tract involvement (Tandaipan et al. 2023).

2.1.4.4 Gastrointestinal involvement

GI tract involvement is a common fibrotic manifestation, affecting of 50–90% SSc patients. All parts of the GI tract can be affected (Forbes et al 2009; Nassar et al 2022). Severe GI involvement affects 8% of SSc patients (Steen et al. 2000). In the pathogenesis, neuronal and smooth muscle dysfunction are the targets of the autoimmune response (McMahan et al. 2023) and atrophy is the primary outcome of the process (Volkmann et al. 2022). In addition, the GI microbiome has been found to be altered in SSc patients even in the early course of the disease, and there are associations with different clinical manifestations like SSc-ILD (Haussmann et al. 2024). GI tract symptoms seem to progress during the time. By assessing the patient-reported symptoms, the female gender, ACA positivity and smoking were risk factors for progression (van Leeuwen et al. 2022). A significant proportion of SSc patients develop a severe GI disease early. In a study by Richard et al. (2019), the percentages were 9.1% at two years and 16% at four years. The definition of a severe GI disease was as: malabsorption, hyperalimentation, pseudo-obstruction and/or > 10% weight loss in association with the use of antibiotics for bacterial overgrowth or esophageal stricture. SSc patients had less than 2 years of disease duration (time from the first non-RP symptom). The severe GI disease was associated with inflammatory myositis, telangiectasias and higher mRSS. The risk of death was over two-fold in patients with severe GI disease, causing significant morbidity.

Table 5 presents the GI manifestations and their frequencies (Nassar et al. 2022). An esophagogastroduodenoscopy (EGD) is used to diagnose gastric antral vascular ectasia (GAVE), and treatment via laser therapy or argon plasma coagulation intervention can be performed. An EGD is also needed to evaluate GI reflux complications and carcinoma. Esophageal dysmotility can be assessed with manometry and sometimes pH monitoring or barium swallowing test are required. The small bowel can be evaluated with an X-ray, CT/MRI and sometimes with capsule endoscopy. Methane and hydrogen breath tests are used to diagnose small intestinal bacterial overgrowth (SIBO) (Marie et al. 2009). A colonoscopy is recommended for new-onset constipation.

There is no evidence that immunosuppression could prevent or treat GI tract involvement. The effect of immunosuppression was analysed in Canadian and Australian patients in order to prevent severe GI tract involvement in early SSc

patients without GI tract involvement at the baseline. The definition of a severe GI tract disease was similar to a study by Richard et al. (2019), but weight loss was defined as 4–10%. Of the 762 patients, 319 were exposed to an immunosuppressive treatment and the rest were not. The immunosuppressants were: MTX (n=169), CYC (n=112), MMF (n=58) and AZA (n=33). Neither biologics nor IVIG were used. No preventive effect of the treatment with immunosuppressants was observed (Richard et al. 2021). Minor evidence was observed with the use of IVIG in a small study. The rapid improvement of SSc-related pseudo-obstruction was detected in three SSc patients (Matsuda et al. 2023).

For upper GI tract involvement PPIs and sometimes H2 blockers are standard care. PPIs are usually required at higher doses than usual. Prokinetics are also an option (Volkmann et al. 2022). In the PROGASS study, the prokinetic drug prucalopride, a 5-HT_4 receptor agonist, significantly relieved GI tract problems. Reflux and bloating reduced, the bowel transit was improved, and the number of complete bowel movements increased (Vigone et al. 2017).

SIBO is common among SSc patients; in addition to lifestyle interventions, rotating antibiotics can be administrated. In a French study, the prevalence of SIBO was 43.1% in 51 SSc patients and it was strongly correlated with digestive symptoms. The eradication of SIBO with rotating antibiotics was successful for 52.4% of the patients. The rotating antibiotics under study were norfloxacin/ metronidazole, which were administered in courses over a three-month period (Marie et al. 2009). Rifaximin is another option for eradicating SIBO. Another study showed that SIBO was more common in SSc patients than control subjects. Eradication was successful in 73.3% of patients with rifaximin, and a significant reduction of symptoms was observed (Parodi et al. 2008). A meta-analysis assessing the efficacy of rifaximin in 1331 patients with SIBO demonstrated an over 70% eradication rate and symptoms relieved in the majority of patients; side effects were rare. This meta-analysis included all patients with SIBO (Gatta et al. 2017).

The treatment of lower GI tract involvement is designed due to the leading symptom, diarrhoea or constipation. Anorectal biofeedback training is an option for treating faecal incontinence (Nassar et al. 2022).

Table 5. Different manifestations and their frequencies in the gastrointestinal tract among patients with systemic sclerosis. Modified from Nassar et al. (2022).

Organ involvement	Prevalence	Gastrointestinal manifestations/complications
Oropharyngeal involvement	10–70%	Microstomia Xerostomia and periodontal disease Gingival inflammation Oropharyngeal dysphagia
Esophageal involvement	90%	GERD Lower esophageal sphincter laxity Esophagitis Esophageal strictures Barrett's esophagus
Gastric involvement	50%	Gastroparesis GAVE Gastric bleeding ectasias Upper GI bleeding
Small bowel involvement	40%	Diarrhoea SIBO Malabsorption Small-bowel pseudo-obstruction Pneumatosis cystoides intestinalis
Colon involvement	20–50%	Constipation Megacolon Large intestine vascular ectasia Lower GI bleeding Wide-mouth diverticula
Anorectal involvement	50–70%	Rectal prolapse Faecal incontinence Faecal impaction
Liver involvement	1.1–1.5%	Primary biliary cholangitis Autoimmune hepatitis

GAVE; gastric antral vascular ectasia, GERD; esophagogastroduodenoscopy, SIBO; small intestinal bacterial overgrowth

Primary biliary cholangitis (PBC) is the most common autoimmune liver disease associated with SSc, and autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) are rarer. The prevalence of PBC is around 2% in SSc patients, and it is associated with lcSSc and ACA positivity (Lepri et al. 2019). The liver disease seems to be milder when it is associated with SSc (Rigamonti et al. 2006). Lepri et al. (2023) compared patients with PBC+SSc and SSc alone from the EUSTAR database. Patients with PBC and SSc had ACA positivity and other autoimmune diseases more frequently, particularly Hashimoto′s thyroiditis. Those

patients also had a milder form of SSc, with less vascular complications, like DUs, PAH and myocardial conduction blocks.

2.1.4.5 Raynaud´s phenomenon and digital ulcers

The most common and usually the first symptom of SSc is RP, sometimes complicated with DUs or pitting scars. Telangiectasias are present in some patients. Ischaemia can result in ulcerations, gangrenes and auto-amputation of the fingertips. Acro-osteolysis due to ischaemia is detectable in the x-rays of hands.

In a study utilising the EUSTAR database of 7655 SSc patients, RP is present in 96.3% of SSc patients and 36% have digital ulcers (DU) during the disease course (Meier et al. 2012). Not only are DUs painful and a cause of disability, but they are also associated with cardiovascular complications and increased mortality (Mihai et al. 2015). In a study comprising patients with very early SSc (VEDOSS), DUs were associated with internal organ involvement and significantly with GI involvement (Bruni et al. 2015). Ischaemia can cause fingertip ulcers, but in those of the extensor part, repetitive microtrauma can cause ulcers. DUs can be associated with calcinosis, and they typically occur on the thumbs, index and middle fingers (Hughes et al. 2017). Digital pitting scars (DPS) typically occur in the fingertips, the presence of which is associated with peripheral ischaemic events, organ involvement and increased risk of death (Hughes et al. 2022).

The cessation of smoking and nicotine products and protection from the cold are essential in the treatment of peripheral vasculopathy. There are many pharmacological treatments available (del Galdo et al. 2024). Calcium channel blockers (CCB) are the first line treatment for RP (Pope et al. 2023). Phosphodiesterase 5 inhibitors (PDE5i), such as sildenafil and tadalafil are an option, and the significant reduction of RP attacks has been detected (Roustit et al. 2013). Intravenous iloprost may be another option in severe RP attacks. Angiotensin II receptor blockers (ARB), aspirin, botulinum toxin, fluoxetine or pentoxiphylline may be another alternative as well. PDE5i demonstrate benefits in healing DUs (Tingey et al. 2013), and they are recommended in the treatment of DUs in addition to iloprost. Bosentan also shows efficacy in preventing new DUs (Matucci-Cerinic et al. 2011) and there is minor evidence that treating DUs with bosentan could reduce the risk of developing PAH (Castellvi et al. 2020). The careful treatment of secondary infections is crucial to prevent osteomyelitis and septicaemia.

2.1.4.6 Pulmonary arterial hypertension

PAH is a manifestation of vasculopathy and leading cause of death among SSc patients in addition to lung fibrosis (Elhai et al. 2017), with typical symptoms

including dyspnoea and fatigue. The prevalence of PAH is around 10% in SSc patients (Mukerjee et al. 2003). The decrease of DLCO in the PFTs is a predictor of the development of pulmonary hypertension (PH) (Steen et al. 2003). Out of SSc specific autoantibodies, ACA, anti-U3 RNP (antifibrillarin), anti-Th/To- antibodies are associated with PAH (Nunes et al. 2018). A study revealed that the majority of SSc-PAH patients had the lcSSc subtype (Goghlan et al. 2018). In another study no difference in the cutaneous subtype of SSc-PAH was observed (Morrisroe et al 2017). It is possible that as lcSSc patients live longer, the prevalence of PAH increases (Pope et al. 2023). PAH typically occurs at the advanced stage of SSc. In addition to PFTs, a six-minute walking test is used at the diagnosis and during the follow-up.

Pulmonary hypertension (PH) is divided in five groups; the main classification is presented in Table 6. SSc- related PAH is included in Group 1. In SSc patients, PH can also be related to ILD, left heart disease or sometimes pulmonary veno-occlusive disease or chronic thromboembolic pulmonary hypertension (Haque et al. 2021). The haemodynamic definition for PH is mean pulmonary arterial pressure (mPAP) >20 mmHg and the definition for PAH also implies pulmonary vascular resistance (PVR) >2 WU and pulmonary artery wedge pressure (PAWP) ≤15 mmHg. The diagnosis of PAH must be confirmed by right heart catheterisation, (RHC) (Humbert et al. 2022).

In the DETECT study of 466 SSc patients with disease duration over three years and DLCO <60%, the prevalence of PAH was 19% (Coghlan et al. 2014). The DETECT algorithm was developed to non-invasively assess the risk of PAH, which showed improved sensitivity with only three (4%) missed PAH cases. When only echocardiography was used, 29% of PAH cases were missed. The clinical and laboratory parameters associated with PAH were: telangiectasias, right axis deviation on electrocardiogram (ECG), ACA positivity, lcSSc subtype, elevated serum urate and NTproBNP. During the study period, the cut-off mPAP for pulmonary hypertension was >25 mmHg, and the threshold was reduced to its current value in 2018. In a Norwegian study of an unselected SSc cohort, patients were divided into whether RHC was performed before or after the institution of DETECT, during the years 2009 through 2013 or 2014 through 2017. The incidence of PAH remained stable, but the frequency of borderline PH (mPAP 20–24 mmHg) increased significantly. Among the diagnosed PAH patients, the frequency of milder cases was pronounced in the latter group (Hoffmann-Vold et al. 2018).

Table 6. The clinical classification of pulmonary hypertension. Modified from Humbert et al. (2022).

Clinical classification of pulmonary hypertension
GROUP 1 Pulmonary arterial hypertension
Idiopathic
Heritable
Associated with drugs and toxins
Associated with other conditions like connective tissue disease
PAH with features of venous/capillary involvement
Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
Heart failure
Valvular heart disease
Congenital /acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung disease and/or hypoxia
Obstructive lung disease or emphysema
Restrictive lung disease
Lung disease with mixed restrictive/obstructive pattern
Hypoventilation syndromes
Hypoxia without lung disease (e.g. high altitude)
Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
Chronic thrombo-embolic PH
Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multifactorial mechanisms
Haematological disorders
Systemic disorders
Metabolic disorders
Chronic renal failure with or without haemodialysis
Pulmonary tumour thrombotic microangiopathy
Fibrosing mediastinitis

PAH; Pulmonary arterial hypertension, PH; Pulmonary hypertension

As new therapies have become available, screening for PAH is crucial. In a French study where PAH detection programme patients were compared to standard monitored patients, a significant reduction of mortality was observed (Humbert et al. 2011). The current guidelines recommend screening for PAH in asymptomatic SSc patients (Humbert et al. 2022).

PAH therapies include CCBs, endothelin receptor antagonists (ERA), PDE5i, guanylate cyclase stimulators (sGC), prostacyclin analogues (PCA) and prostacyclin receptor agonists (PRA). The 2022 European Society of Cardiology (ESC)/ERS guidelines recommend combination therapy with ERA+PDE5i for low- or intermediate- risk patients and combination therapy with ERA+ PDE5i+ i.v/s.c PCA for high-risk patients without cardiopulmonary comorbidities. For patients with cardiopulmonary comorbidities, initial oral monotherapy with PDE5i or ERA is recommended (Humbert et al. 2022). The initiation of diuretics, warfarin and so forth should be considered. Lifestyle interventions, cessation of smoking and nicotine products, vaccines and oxygen supplementation are part of the treatment as well.

The importance of early treatment with combination therapy was observed in the AMBITION study. It was event driven, double-blind study, where patients were 2:1:1 randomised to receive ambrisentan (ERA)/tadalafil (PDE5i), ambrisentan/ placebo or tadalafil/placebo. Patients were divided into functional class II (FC II) and III (FCIII). The combination therapy was more effective than pooled monotherapy, as the reduction of clinical failure events was 79% in FCII-, and 42% in FCIII groups, respectively. Less severe ill patients benefitted even more from the combination therapy and no hospitalisation for worsening PAH in that group was observed (White et al. 2019). In a CTD-PAH study utilising the European pulmonary hypertension registry (COMPERA), SSc-PAH patients had the highest mortality risk compared to other CTD-PAH patients; the 1-, 3-, and 5-year survival estimates were 85%, 59%, and 42%, respectively. The initial combination therapy with ERA+PDE5i improved prognosis compared to patients treated with a monotherapy of either drug, 5-year survival rates were 61% for dual therapy, 41% for ERA monotherapy and 37% for PDE5i monotherapy (Distler et al. 2024).

To date, there is no clear evidence of immunosuppression in the treatment of SSc-PAH. A small RCT studied the efficacy of RTX compared to the placebo in the early, isolated SSc-PAH group. The study consisted of 57 patients and a 6-minute-walk distance improved significantly in 48 weeks; the tolerability of RTX was good (Zamanian et al. 2021). In the Turkish retrospective study of 547 SSc-PAH patients, patients treated with immunosuppressants had higher survival rates (Sari et al. 2024).

2.1.4.7 Primary heart involvement

The prevalence of primary heart involvement, a common determinant of mortality among SSc patients, is unclear but estimated to be between 15% and 35% (De Luca et al. 2024). It accounts of 12% deaths in the EUSTAR cohort (Elhai et al. 2017). Inflammation of the myocardium leads to fibrosis, and heart failure and conduction blocks in advanced cases. Diastolic dysfunction due to myocardial fibrosis is typical. It is hypothesised that pHI results from small vessel vasculopathy in the heart (Bruni

et al. 2021) SSc-pHI can remain asymptomatic. Pericarditis is one SSc manifestation in the heart. SSc-pHI usually requires a multidisciplinary approach to distinguish it from secondary causes like coronary artery disease. In the consensus of the UK Systemic Sclerosis Study group, the risk factors for SSc-pHI were identified: male gender, dcSSc subtype, ATA positivity together with rapid skin thickness progression, anti-Ku-, anti-Histone (AHA)-, anti-RNA polymerase and anti-U3-RNP antibodies, presence of tendon friction rubs, DUs, ILD, myositis and higher HAQ-Disability Index scores (Bissel et al. 2017).

Diagnostic modalities include ECG, echocardiography, cardiac magnetic resonance imaging (CMR), endomyocardial biopsy, single photon emission computed tomography (SPECT), and exercise testing. An echocardiography detects pericardial effusions and CMR detects abnormalities in the myocardium. Coronary angiography and RHC are needed for a differential diagnosis. The most frequently used biomarkers are Troponins I and T, B-type natriuretic peptides (BNPs) like N-terminal prohormone BNP (NT-proBNP) and creatine kinase (Bissel et al. 2017; Bruni et al. 2021; De Luca et al. 2024). The World Scleroderma Foundation/Heart Failure Association´s consensus for the screening, diagnosis and follow-up assessment of SSc-pHI was published in 2023.The presence of SSc-pHI should be screened in every patient with a new SSc diagnosis. Among the previously mentioned biomarkers, an ECG and a transthoracic echocardiography should be performed at baseline and annually for all patients. For asymptomatic high-risk patients Holter may be considered. CMR may be considered case-by-case and for all patients with a suspicion of pHI. If CMR remains normal, an endomyocardial biopsy should be considered. A multidisciplinary team assessment is needed for symptomatic patients and those with diagnosed SSc-pHI (Bruni et al. 2023).

Immunosuppression is crucial in the treatment of SSc-pHI, although no guidelines have yet been established. Alongside conventional cardiologic therapy, treatments for vasculopathy are typically needed. CCBs have shown benefit in preventing cardiac dysfunction, and they should be prescribed if there are no contraindications. In the study of SSc patients, a 14-day of nifedipine treatment improved myocardial perfusion and function (Vignaux et al. 2005). There are only small studies and case reports published in the immunosuppressive treatment of SSc-pHI (Batani et al. 2024; Ferlito et al. 2022). Glucocorticoids, AZA, MMF, CYC, RTX, TCZ and IVIG could be beneficial in treating inflammation. There is minor evidence that nintedanib could have efficacy in SSc-pHI (De Luca et al. 2024). Arrhythmia prevention and the consideration of an implantable defibrillator is part of the treatment as well.

2.1.4.8 Scleroderma renal crisis

Scleroderma renal crisis (SRC) is a life-threatening manifestation of SSc. The prevalence has decreased from 20% to 5% and it is strongly associated with the dcSSc subtype. The one-year mortality is over 30% and 25% of patients remain dependent on the dialysis (Hudson et al 2021). On the other hand, Steen et al. (2007) reported a remarkable increase in the 5-year survival of SRC after the introduction of ACEi, from <10% to 65%. Around one third of patients can be removed from dialysis within two years after the onset of SRC (Mouthon et al. 2014).

SRC occurs typically at the early stage of the disease, as 75% of cases occur within the first four years of the symptom attributable to SSc. Endothelial cell injury leads to intimal thickening and proliferation and narrowing of the lumen of the vessels. The blood flow decreases, and the activation of renin-angiotensin axis occurs. Simultaneously, fibrin production and platelet aggregation increase and result in microangiopathic haemolytic anaemia. The administration of glucortocoids (>15 mg/day prednisone) can trigger SRC (Steen 2003). The clinical signs include increased blood pressure (>140/90 mmHg) or a rapid increase in blood pressure compared to the baseline, combined with an increase in serum creatinine and a ≥ 30% decrease in the glomerular filtration rate. Proteinuria, haematuria, thrombocytopenia, haemolysis, congestive heart failure, hypertensive encephalopathy and seizures can also be present. Around 10% of SRC cases are normotensive, and those patients are more often exposed to glucocorticoids and two-thirds have thrombotic microangiopathy (Mouthon et al. 2014). A renal biopsy is sometimes needed to confirm the diagnosis as SSc patients can present other renal diseases. High blood pressure or thrombocytopenia may be a contraindication to the biopsy (Cole et al 2023).

Several risk factors, in addition to the dcSSc subtype for SRC have been identified. Anti-RNAPol3 antibodies are associated with an increased risk for SRC (Moinzadeh et al 2020; Mouthon 2014). In a German study of 2873 SSc patients only 70 (2.4%) developed SRC. Cutaneous subtypes were divided as follows: dcSSc 57.1%, lcSSc 31.4% and overlap syndrome 11.4%. Independent risk factors for SRC were anti-RNAPol3 antibodies, prior proteinuria, diminished DLCO and prior hypertension (Moinzadeh et al. 2020).

In the treatment of SRC, the rapid administration of ACEi is crucial, but the prophylactic use of them can be harmful. A study found that the 1-year mortality after the onset of SRC was two-fold for patients with the prior use of ACEi (Hudson et al 2014). Additional anti-hypertensive drugs, like CCBs or ARBs, should be used to control blood pressure. Intravenous vasodilatators may be needed as well and betablockers and diuretics are not recommended. Renal replacement therapy is required for 60% of patients and plasma exchange is used in the suspicion of thrombotic thrombocytopenic purpura (TTP) (Cole et al 2023).

2.1.4.9 Calcinosis of soft tissues

Calcinosis of skin and soft tissues is common among SSc patients, causing a significant burden for them. In SSc patients, dystrophic calcinosis in soft tissues occurs despite normal blood levels of calcium and phosphorus and it is associated with autoimmune diseases. The chemical form of crystals is calcium hydroxyapatite (Avanoglu-Guler et al. 2024). Calcinosis occurs in 18–49% of SSc patients. Risk factors for its development are longer disease duration, older age, digital ischaemia, late capillaroscopic pattern, ACA, anti- RNAPol3 and anti-PM/Scl antibody positivity. In the pathogenesis of soft tissue calcinosis, chronic ischaemia, hypoxia-related markers, inflammation and mechanical stress play a role. Typical areas for calcinosis are the hands and knees, especially the index finger and thumb due to recurrent microtrauma, sometimes they can occur elsewhere in the body. Calcinosis typically causes pain and skin ulceration which can be complicated by secondary infections, but they can also cause pain by the compression of neural structures. The extent of calcinosis can be assessed by different imaging modalities: x-ray, CT, MRI and US.

There is no approved treatment for calcinosis (Avanoglu-Guler et al. 2024; Davuluri et al. 2023), and randomised controlled studies are lacking. Moreover, treatment options are divided into local and systemic treatments. Local treatments are divided further into topical, intralesional and surgical treatments. The timing of surgical treatment is important in preventing larger damage to, e.g. neural structures. Topical and intralesional sodium thiosulfate have been beneficial for patients in small studies. Minor evidence has been reported concerning a few systemic treatments, which include CCBs, RTX, minocycline and colchicine (Avanoglu-Guler et al. 2024).

Table 7 summarizes the latest EULAR 2023 recommendations for the treatment of SSc by different manifestations and the strength of their evidence.

Table 7. EULAR 2023 recommendations for the treatment of different manifestations of systemic sclerosis. Modified from del Galdo et al. (2025).

Manifestation	Strength of recommendation			
	A	**B**	**C**	**D**
Raynaud's phenomenon	CCB PDE5i Iloprost			
Digital ulcers	PDE5i Bosentan Iloprost			
Pulmonary arterial hypertension	PDE5i+ERA Iloprost	Riociguat Selexipag	No warfarin	
Musculo-skeletal				MTX
Skin fibrosis	RTX MTX	MMF	TCZ	
Interstitial lung disease	RTX MMF CYC Nintedanib	TCZ		
Gastro-intestinal		PPI	Prokinetics	Antibiotics
Renal crisis		No ACEi for prevention	ACEi	

ACE; angiotensin convertin enzyme, CCB; calcium channel blocker, CYC; cyclophosphamide, ERA; endothelin receptor antagonist, MMF; mycophenolate mofetil, MTX; methotrexate, PDE5i; phosphodiesterase five inhibitor, PPI; proton pump inhibitor, RTX; rituximab, TCZ; tocilizumab.

2.1.5 Comorbidities

2.1.5.1 Concomitant autoimmune diseases

The occurrence of concomitant autoimmune diseases is common in SSc patients. Autoimmune diseases can be divided into overlap SSc, where SSc occurs simultaneously with other connective tissue diseases, and/or other autoimmune diseases. The disease is considered as overlap SSc, when manifestations of another CTD occur more frequently than what is generally observed in SSc patients. These manifestations include arthritis, myositis and sicca syndrome.

A systematic review analysed polyautoimmunity among SSc patients and in which 6102 patients were included. The following autoimmune diseases were assessed in the study: SjD, dermatomyositis/polymyositis (DM/PM), rheumatoid

arthritis (RA), systemic lupus erythematosus (SLE), autoimmune thyroid disease and PBC. Overall, 25.7% had one or more and 3.9% had at least two simultaneous autoimmune diseases. The most common concomitant autoimmune disease was autoimmune thyroid disease (10.4%), followed by SjD (7.7%) and dermatopolymyositis/polymyositis (5.6%). The weighted prevalence of PBC was 3.0%. The patients with a concomitant autoimmune disease were more frequently women (92.8% vs 86.8%) and had lcSSc (81.6% vs 64.3%) compared to those without other autoimmune diseases. The patients with simultaneous SjD and PBC had lcSSc significantly more often and the latter had more ACA positivity more frequently (81.3% vs 34.7%). The difference in the cutaneous subtype was not observed in patients with concomitant RA or dermatopolymyositis/polymyositis (Elhai et al. 2013).

In a British study comprising 1700 SSc patients, 332 (20%) had SSc overlap syndrome. There was no difference in the cutaneous subtype of the overlap syndrome group compared to others. Of these patients, 35 had three or more CTDs, and the rest 297 patients had 2 overlapping CTDs. The most common overlap disease was myositis 127/297 (42.8%) followed by RA 95/297 (32%), SjD 50/297 (16.8%) and SLE 25/297 (8.4%). The diffuse cutaneous subtype was observed in 40.2% of SSc/myositis overlap patients. ANA positivity was observed in 96.6% of overlap patients and ACA and SSA positivity were the most common among SSc/SjD overlap patients. U1RNP positivity was the most common in SSc/SLE overlap patients and polymyositis-scleroderma (PM/Scl) antibody positivity in SSc/myositis patients (Pakozdi et al. 2011).

In a two-centre study from France encompassing 534 SSc patients, 34 (6.4%) had overlap SSc. The most common overlap disease was RA 21/534 (3.9%), followed by SjD 14/534 (2.6%) and SLE 4/534 (0.7%). Five patients had two overlap CTDs. There was no difference in the cutaneous subtype or the disease-related complications between overlap SSc and non-overlap SSc patients. Patients with overlap SjD had higher mortality. Overlap SSc patients received more corticosteroids, immunosuppressive drugs and biologics (Scherlinger et al. 2021).

2.1.5.2 Cardiovascular disease

Due to a presence of macrovascular involvement in SSc patients (Matucci-Cerinic 2013), the risk of cardiovascular disease is increased. Early morphological and functional atherosclerotic changes have been detected more often in SSc patients than controls attributable to macrovascular involvement (Meiszterics et al. 2016). In an Italian study of 613 SSc patients, clinical and subclinical atherosclerosis was present in 9.3% and 37.1% of patients, respectively. These numbers were higher than in the general population and were independently associated with traditional risk

factors and SSc-specific features. Subclinical atherosclerosis was assessed by doppler ultrasonography (Liakouli et al. 2024). A population-based cohort study from the UK comprised 865 SSc patients and their matched controls. The risk of myocardial infarction and stroke was approximately two-fold, and the risk of peripheral vascular disease was over four-fold after adjusting for traditional cardiovascular risk factors (Man et al. 2013). An increased risk for cardiovascular disease was reported in a meta-analysis. The pooled hazard ratios for cardiovascular disease, peripheral vascular disease, myocardial infarction and stroke were 2.36, 5.27, 2.36, and 1.52, respectively (Cen et al. 2020).

2.1.5.3 Malignancies

The risk of cancer is increased in SSc patients, especially for lung cancer and haematological malignancies. In a meta-analysis of over 7000 patients, the risk ratio for cancer was 1.75 for SSc patients (Bonifazi et al. 2013). In an Australian study of 1727 SSc patients, the cancer risk was over two-fold. The most common cancers were breast, melanoma, hematologic and lung cancer. Anti-RNAPol3 antibodies were associated with breast cancer and melanoma within the first five years after SSc onset. Lung cancer was associated with ILD but not with the duration of SSc (Morrisroe et al. 2020). A Canadian study analysed the association of cancer and autoantibodies among 1698 SSc patients. The most frequent malignancies within 2 years were breast-, gynaecological and haematological cancers. The positivity of ATA and U1-RNP-antibodies increased the risk of these malignancies, while RNAPol3-antibody positivity did not (Hoa et al. 2022). A British study, which identified 1588 SSc patients, assessed the risk of malignancy associated with SSc compared to the background population. The risk of malignancy increased 40% in SSc patients and the all-cause mortality was three-fold. The most common malignancies were cancers of the skin, lung and breast (Pauling et al. 2025).

In a Chinese study of 838 SSc patients, 12 patients with lung cancer were diagnosed. Out of these 12 patients, who all were females and non-smokers, 8 had a prior ILD diagnosis. Nine cancers were adenocarcinomas, one squamous cell carcinoma, small cell lung carcinoma and carcinoma not otherwise specified were detected (Chen et al. 2020).

2.1.6 Prognosis and causes of death

SSc is a severe disease with increased morbidity and mortality (Denton et al. 2017). Mortality is the highest among rheumatic diseases (Steen et al. 2007; Elhai et al. 2017). The studies assessing changes in mortality are controversial. One study compared two SSc cohorts of 520 patients, where cohorts were divided by the

disease onset to cohorts of the years 1990–1993 (n=234) and 2000–2003 (n=286). The 5-year survival improved in the group of dcSSc from 69% to 84%, but there was no difference in the group of lcSSc patients. Lung fibrosis and PAH were detected more often in the latter cohort (Nihtyanova et al. 2010). Another study analysed changes in the causes of death and survival during the years 1972 through 1997, divided in 5-year intervals. Both dcSSc and lcSSc patients were included. The ten-year survival increased from 54% to 66% during the study period. SRC was the most common cause of death in the early years but during the follow-up, cardiopulmonary causes became the most common causes of death (Steen et al. 2007). A Swedish study assessed the survival of SSc patients between 2004 and 2015. The five- and ten-year survival rates were 79.8% and 67.7%, respectively. These rates were significantly lower than the general population (Bairkdar et al 2023).

In a meta-analysis the pooled standardised mortality ratio (SMR) was 2.72 compared to the general population. The estimates of cumulative survival for 5 years and 10 years were 74.9% and 62.5%, respectively. While an improving trend was observed in the latest studies, it did not reach statistical significance. The majority of patients died due to SSc-related causes, with pulmonary involvement being the most common cause (Rubio-Rivas et al. 2014). Another meta-analysis analysed the trend in mortality in SSc patients over 40 years, from 1960 to 2010. The study comprised 9 studies with a total of 2691 SSc patients and 732 deaths. The pooled SMR was 3.53 and no significant improvement in the prognosis was observed. The most common causes of death were cardiac followed by lung involvement (Elhai et al 2012).

In a study encompassing a cohort of French SSc patients and the EUSTAR database, the causes and risk factors of death were analysed. Primary heart disease, including both PAH and pHI, was the most common cause of death, accounting for approximately 30% of deaths. The second most common cause of death was ILD. The risk score predicting the three-year mortality was developed using a multiple variable analysis. Factors associated with low survival were older age, male gender, dcSSc subtype, SRC, prominent dyspnoea, DUs, contractures, muscle weakness, elevated CRP, proteinuria, left ventricular ejection fraction <50%, ILD, DLCO <60% predicted and FVC<70% of predicted. The different weight was assessed for different variables (Elhai et al. 2017). Another study was conducted from the EUSTAR database: among 5860 SSc patients, 284 deaths occurred. Questionnaires were obtained from 234 deaths; SSc-related causes were the most common with 55% of deaths. Of those, 35% died due to lung fibrosis, 26% to PAH and 26% to cardiac causes. Among the non-SSc-related causes approximately 30% were due to infections, malignancies and cardiovascular disease. The independent risk factors of death were proteinuria, PAH, decreased FVC (<80%), dyspnoea (NYHA class 3 or 4), age at the onset of RP, lower DLCO and higher mRSS (Tyndall et al. 2010).

2.2 Localized scleroderma

2.2.1 Pathogenesis

Although morphea and SSc share similar pathogenetic pathways, they are distinct diseases, as morphea is not associated with internal organ involvement. The environmental factors may trigger the disease in genetically predisposed subjects. These environmental factors may be viruses, local trauma, surgery, radiation and vaccines (Papara et al. 2023). The excess collagen production is a result of a vascular endothelial injury and the production of profibrotic cytokines (Teske et al. 2024). Skin biopsies of morphea patients have revealed a subpopulation of fibroblasts responsible for the excess production of collagen (Kähäri et al. 1988).

2.2.2 Clinical manifestations and diagnosis

Localized scleroderma ie. morphea is a rare autoimmune disease primarily affecting the skin. The plaques in the skin are red or violaceous in colour, later changing to white atrophic lesions (Seghal et al. 2002). The plaques may occur at the neck, head, trunk and extremities. Sometimes inflammation and fibrosis of the skin can spread to the underlying tissues and these extracutaneous manifestations are more common in certain subtypes of morphea. Sclerodactyly, RP and NVC changes do not occur (Fett et al. 2011). Morphea does not spread to visceral organs, transition to SSc does not occur and morphea is typically not associated with life-threatening complications. The morbidity is significant and relapse rates are high, in approximately 25% of morphea patients. Children have a higher risk of relapse than adults (Papara et al. 2023).

Histopathology is usually needed to confirm the diagnosis, though it cannot distinguish morphea from SSc (Fett et al. 2011). The skin biopsy should be deep enough as the morphea sometimes affects the fascia and muscle, and it can provide details of the disease stage. In the histopathology of the active morphea lesion, inflammatory lesions on the perivascular and periadnexal area are detected. Primarily composed of lymphocytes, these infiltrates may extend to the subcutaneous fat. In late stage morphea lesions, increased collagen is observed without any sign of inflammatory cells (Florez-Pollack et al. 2018).

No diagnostic laboratory tests are available for morphea. In addition to the baseline routine tests, such as blood count, kidney and liver tests, it is typically recommended to evaluate ANA and extractable antinuclear antigen antibodies (ENA). ANA and ENA are tested once to exclude SSc. While the European Dermatology Forum (EDF) guidelines (Knobler et al. 2024) do not recommend a routine screening of ENA, in Finnish clinical practice, it is part of the laboratory

testing for morphea patients. Eosinophilia is usually associated with eosinophilic fasciitis. Creatine kinase can be screened in case of muscle involvement. As routinely testing for *Borrelia burgdorferi* is currently not recommended (Knobler et al. 2024), it should only be performed in clinically suspicious cases (Papara et al 2023).

Imaging methods can provide additional information on the extent of inflammation. MRI is recommended for all patients with involvement in the face, neck and head, as it may enable abnormalities in the intracranial area to be revealed. Other imaging methods are ultrasonography, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), thermography and dermoscopy (Papara et al. 2023). These methods, excluding dermoscopy and ultrasonography, are rarely used in clinical practice.

The remission of morphea usually occurs after three to five years. However, the recurrence rate of morphea is relatively high. The recurrence rate was studied in 344 morphea patients (Mertens et al. 2015); of these patients, 119 (35%) had pediatric-onset and 225 (65%) adult-onset morphea, respectively. The majority were females, as the female to male ratio was 2.8:1 in both pediatric-onset and adult-onset groups. Linear morphea was the most common in the pediatric-onset group, and plaque type was the most common among adults. The median follow-up times for pediatric-onset and adult-onset patients were 38 months and 18 months, respectively. The disease recurrence occurred in 27% of pediatric-onset patients and 17% of adult-onset patients. The recurrence was most associated with linear morphea of the limbs.

In assessing the activity of morphea and response to treatment, validated tools have been developed. The localized scleroderma assessment tool (LoSCAT) measures 18 anatomic sites of the skin. Both severity and damage are assessed by using the modified Localized Skin Severity Index (mLOSSI) and Localized Scleroderma Damage Index (LoSDI). These methods are currently used only in clinical trials, not in clinical practice. The severity assessment includes erythema, skin thickness, new lesion or lesion extension. The damage assessment includes dermal or subcutaneous atrophy and dyspigmentation (Kelsey et al. 2013).

2.2.3 Epidemiology

Peterson et al. (1997) studied the epidemiology of morphea from 1960 to 1993 in Olmsted County Minnesota in which a total of 1030 patient records were screened. The annual incidence rate was 2.7 per 100 000 inhabitants and a significant increase was detected during the study period. The increase was on average 3.6% per year, and the survival rate was similar to the general population. Meanwhile, a study from the UK determined that the prevalence rates were 13 and 48 per million inhabitants for males and females, respectively. The annual incidence rates were 1 and 6 per

million inhabitants, respectively (Silman et al. 1988). Morphea is more common among females than males, as the female to male ratio is 4-6:1 (Silman et al.1988, Papara et al. 2023). It is also more common among the white race than other races (Fett et al. 2011). The incidence has two peaks, one in childhood at ages between 2 and 14 years and another one in middle-age (Papara et al. 2023). In children, morphea is ten times more common than SSc (Murray et al. 2002).

2.2.4 Subtypes of localized scleroderma

The EDF has proposed the classification of morphea by clinical presentation (Knobler et al. 2024), with Table 8 presenting the main types and their subtypes.

The most common type of limited morphea is *plaque morphea*, characterised by oval-shaped lesions that may become sclerotic and may cause hair loss. Lesions are typically located in the trunk. In the *guttate type of limited morphea*, the small yellowish or whitish sclerotic lesions have a shiny surface, and they are typically located on the trunk. *Atrophoderma idiopathica of Pierini and Pasini* is superficial morphea. Typically located on the trunk or extremities these patches are symmetrical and sharply demarcated, hyperpigmented and non-indurated.

Generalized morphea is defined as existing four or more plaques that are three centimetres or more in size and involve two or more anatomic sites. These seven anatomic sites are head-neck, each extremity, anterior and posterior trunk. Lesions typically occur symmetrically and tend to coalesce. A rare form of the generalized type is disabling *pansclerotic morphea,* which is a severe disease. Inflammation extends to the underlying tissues, fat, fascia, muscle and bone. Severe contractures among ulcerations and necroses of the skin can also occur.

Linear morphea is the most common form in children. Deep involvement in the underlying tissues is common. It may occur on limbs, where lesions are band-shaped, and on the face (en coup de sabre and Parry-Romberg syndrome).

In the deep type of morphea, the inflammation in plaques extends to deep tissues even in the muscles. In the mixed type, which typically occurs in children, there are both plaques and linear morphea.

For eosinophilic fasciitis, the onset is usually rapid with swelling of the skin. In the later stages, indurated and fibrotic lesions occur. It is predominantly located on the extremities.

Table 8. The types and subtypes of morphea by EDF classification.

Type of localized scleroderma
Limited morphea
Plaque morphea
Guttate morphea
Atrophoderma idiopathica of Pierini et Pasini
Generalized type
Generalized morphea
Disabling pansclerotic morphea
Linear type
Linear morphea of the extremeties
Linear morphea “en coup de sabre”
Progressive facial hemiatrophy (Parry-Romberg syndrome)
Deep type
Mixed type
Eosinophilic fasciitis (Shulman syndrome)

EDF; European Dermatology Forum

2.2.5 Autoimmunity

2.2.5.1 Autoantibodies

In clinical practice and according to the EDF guidelines, SSc-specific antibodies or other ENA antibodies are not seen in morphea patients. While ANA can sometimes be positive in morphea, it usually happens in cases of linear morphea in children in up to 40% of these patients (Knobler et al. 2024). ANA positivity with older age at the time of diagnosis and the absence of extracutaneous manifestations predicted the disease relapse in children (Kurzinski et al. 2019). On the other hand, ANA positivity was not associated with disease recurrence in 344 adult-onset and pediatric-onset patients (Mertens et al. 2015). In the literature, ANA and ENA are, in rare cases, described to be detected in adult morphea patients (Leitenberger et al. 2009; Rosenberg et al. 1995; Zulian et al. 2006). However, positivity for these autoantibodies is associated with deeper skin involvement and extracutaneous manifestations.

2.2.5.2 Concomitant autoimmune disease

Autoimmune diseases occurring simultaneously in morphea patients and their relatives is common. In a study encompassing 245 adult and pediatric morphea

patients, concomitant autoimmune diseases were common. Among all morphea patients, 18% had a concomitant autoimmune disease. They were more common among adults than children (29% vs 3%); of these concomitant autoimmune diseases, the most common ones were psoriasis and alopecia areata. Familiar autoimmune diseases were more common among pediatric-onset patients than adult-onset morphea patients (22% vs 11%) (Leitenberger et al. 2009). Concomitant autoimmune diseases were also common among 34 patients with a head variant of linear scleroderma; any simultaneous autoimmune disease occurred in 8 (23.5%) patients (Fan et al. 2023). In a recent study of 128 morphea patients, simultaneous autoimmune diseases were common, the most common of which were hypothyroidism (14.8%), genital LSA (8.6%), SjD (4.7%), RA (3.9%) and psoriasis (2.3%) (Abdusalamova et al. 2025).

SSc occurring simultaneously is rare, ranging from 2.4% to 7.4% (Vanhaecke et al. 2020). In the study by Peterson et al. (1997), none of the 1030 patients progressed to SSc and no internal organ involvement was observed. In an Italian study, only 8 (2.4%) of 330 SSc patients had these two conditions simultaneously. All SSc subtypes were lcSSc (Giuggioli et al. 2018).

2.2.6 Malignancies

The risk of cancer is increased in SSc, though such data of morphea patients is limited. In a study of 204 morphea patients over a 11-year follow-up period, 23% of patients were diagnosed with cancer. The occurrence was almost equal before and after the morphea diagnosis. The most common pre-morphea cancer was breast cancer, while the most common post-morphea cancer was non-melanoma skin cancer (Lyakhovitsky et al. 2024). The increased risk of melanoma and non-melanoma skin cancers has been observed in a study with 1448 morphea patients. When compared to the background population, the risk of melanoma, squamous cell carcinoma and basal cell carcinoma was 6.6-, 12.8-, and 13.1-fold, respectively. This could be partly explained by the use of systemic immunomodulatory treatments and phototherapy (Boozalis et al. 2019).

2.2.7 Extracutaneous manifestations

In an older study of morphea patients, the extracutaneous manifestations were more common in the linear and deep subtypes. The most common extracutaneous manifestation is musculoskeletal (Peterson et al. 1997). In a study of 750 juvenile morphea patients, 168 patients (22.4%) had one or more extracutaneous involvements; altogether, 193 extracutaneous manifestations were detected. Articular involvement was the most common (47.2%) followed by neurologic

(17.1%), vascular (9.3%), ocular (8.3%), gastrointestinal (6.2%), respiratory (2.6%), cardiac (1%) and renal (1%) involvements (Zulian et al. 2005). Intracranial findings of the children with head variants of linear morphea were studied by using CT or MRI. Twenty-four patients had the en coup de sabre (ECDS) variant and eight had a Parry-Romberg Syndrome (PRS) and ECDS overlap. Intracranial abnormalities were detected in 19% of patients, half of which were asymptomatic. Overall, this justifies a routine MRI-screening of all morphea patients with lesions in the head, face and neck area (Chiu et al. 2012).

2.2.8 Differential diagnosis

The histopathology of the skin is typically needed to confirm the diagnosis of morphea. It is typically difficult to differentiate it from other diseases affecting the skin especially at the early stage of the disease.

While a biopsy of the skin cannot differentiate it from SSc, clinical findings are different. In SSc, RP is typically present, and sclerodactyly, telangiectasias and thickening of the skin on the face are typical findings. Internal organ involvement also occurs frequently in SSc.

Lichen sclerosus (LSA) frequently occurs simultaneously in patients with morphea and extragenital involvement may occur. The histopathology can differentiate these two conditions. In a Finnish study, 455 female patients with LSA were analysed and 1.3% had morphea concomitantly (RR 60, CI 19.2–187) (Hieta et al. 2021).

Table 9 presents the diseases and conditions that should be considered in the differential diagnosis of morphea in different subtypes.

Table 9. The differential diagnostic conditions of morphea. Modified from Knobler et al. (2024).

Limited morphea Inflammatory phase	**Limited morphea Late stage Hyperpigmentation**	**Limited morphea Late stage Atrophy**	**Limited morphea Late stage Sclerosis**	**Generalized Morphea**	**Linear Morphea**
Atopic eczema Lichen sclerosus Erythema migrans Cutaneous mastocytosis Granuloma annulare Mycosis fungoides Drug-related reactions Chronic radiation dermatitis Porokeratosis Mibelli	Drug-related reactions Post-inflammatory hyperpigmentation Lichen planus actinicus Café-au-lait spots Erythema dyschromic. perstans	Acrodermatitis chronica atrophicans Lipodystrophy Lichen sclerosus Atrophic scarring	Necrobiosis lipoidica Pretibial myxodema Spontaneous keloid	Systemic sclerosis MCTD Pseudo-sclerosderma Scleredema adultorum Sclero-myxedema Chronic graft-versus-host disease Nephrogenic systemic fibrosis Porphyria cutanea tarda	Panniculitis Lupus erythema-thosus profundus Progressive lipodystrophy Localized lipodystrophy Focal dermal hypoplasia Steroid atrophy

MCTD; Mixed connective tissue disease

2.2.9 Treatment

2.2.9.1 Topical treatment

In determining the therapeutic options, the activity, extent and depth of the lesions should be considered. Sometimes physiotherapy and surgical treatments are needed in addition to the main treatment.

Topical treatments demonstrate efficacy in limited plaque morphea but not in the deeper subtypes of the disease. Topical corticosteroids and calcineurin inhibitors are primarily recommended, and calcitriol and imiquimoid can be used. Moderate-to high-potency glucocorticoids are recommended in the active phase, but their regular use should be limited to a total of three months. Interval or proactive therapy may be used afterwards (Knobler et al. 2024).

Tacrolimus is a calcineurin inhibitor and by inhibiting T-cell activation it is an anti-inflammatory agent. A small randomised, double-blind pilot study was conducted by Kroft et al. (2009) using topical tacrolimus 0.1% in comparison with petroleum emollient in ten active morphea patients. A significant improvement of

morphea plaques was observed in the tacrolimus group clinically and by using durometer. Moelleken et al. (2022) described a patient with severe ulcerative morphea, who was treated successfully with topical pimecrolimus, another calcineurin inhibitor. This patient was previously treated with phototherapy and systemic therapy with poor results.

Topical calcipotriol is recommended in active, superficial lesions, and topical imiquimod is found to be beneficial in skin indurations (Knobler et al. 2024).

2.2.9.2 Systemic treatment

MTX with or without systemic glucocorticoids is used particularly in linear, generalized and deep subtypes of morphea, and these are the first-line treatment options in eosinophilic fasciitis. MTX was efficacious and well-tolerated among 70 children aged 6–17 years in a double-blind, placebo-controlled trial. The study population consisted of newly diagnosed patients; the mean disease duration was 2.3 years. Patients were randomised 2:1 to receive MTX in addition to glucocorticoids or glucocorticoids alone. The relapse rate and the appearance of new lesions were significantly lower in the MTX group; 32.6% vs 70.8% and 6.5% vs 16.7%, respectively. The skin score rate and target lesion temperature decreased significantly in the MTX group. The side effects were mild, and no treatment discontinuations occurred (Zulian et al. 2011). In a small study on adult patients with widespread morphea, they were treated successfully with low-dose MTX. A study consisted of nine patients and the treatment period lasted 24 weeks (Seyger et al. 1998). MTX was the most common systemic treatment in German morphea patients (Abdusalamova et al. 2025).

Not only is MMF commonly used in SSc, but it is also beneficial particularly in SSc-ILD and in skin fibrosis. For MTX-intolerant or -resistant morphea patients, MMF could be an option for systemic treatment (Arthur et al. 2020; Martini et al. 2021). Arthur et al. (2020) studied the efficacy of MMF in 77 patients with severe morphea, the most common subtype of which was generalized morphea. The majority of patients were treated with a prior immunosuppressive therapy; 65 out of 77 (84%). The most common treatment was MTX. At the 9-to-12-month follow-up, the majority (87%) of patients had a stable or improved disease and 35% achieved remission. Twelve patients discontinued treatment due to adverse effects; GI tract side effects were the most common, followed by infections and cytopenias.

Another study analysed the efficacy of MMF in pediatric patients. The efficacy of MMF on MTX resistant or intolerant patients was compared to MTX-treated patients. Altogether, 22 patients received MMF with (n=12) or without (n=10) concomitant MTX and 47 patient received MTX. Glucocorticoids were used in both groups. Pansclerotic and mixed morphea patients occurred more often in MMF

groups and linear scleroderma of the face was slightly more common in MTX treated patients. Otherwise, no demographical differences between the groups were observed. MMF was well-tolerated and effective in MTX refractory patients, and no significant difference between the groups was observed. Combination therapy and monotherapy were equally effective (Martini et al. 2021).

Hydroxychloroquine (HCQ), an antimalarial drug, is a widely used immunomodulatory agent in various dermatological disorders, and it is generally well-tolerated. Currently, HCQ is rarely used in the treatment of morphea. The efficacy of HCQ was retrospectively studied in 84 morphea patients over a period at least six months. The majority were females, 65 out of 84 (77.4%) and 50 (59%) were adult-onset morphea patients and the rest were pediatric-onset patients. The response to HCQ was good: 36 (42.9%) patients had complete response and 32 (38.1%) had partial response over 50%. The side effects were mild, with nausea the most common (Kumar et al. 2019).

The use of biologics is rising in morphea patients due to the increasing evidence of their efficacy. In a recent review of studies involving patients with juvenile morphea and SSc patients, the efficacy of biologics was evaluated. The number of treated patients was small, and 17 articles of 58 pediatric morphea patients were reviewed. The most used biologic agents were abatacept, ABA (55.2%) and tocilizumab TCZ (48.3%). The main indication for biologic drugs was progressive or resistant skin fibrosis. The majority of patients were treated previously or concomitantly with immunosuppressive drugs and for 22 (36.7%) patients, a biologic drug was used as a monotherapy during the treatment. Improvement was observed in 92.9% for ABA and 77.4% for TCZ, respectively. Biologic drugs were well-tolerated among children (Sener et al. 2025).

The current guidelines recommend MTX with or without glucocorticoids as a first-line systemic therapy. MMF is considered a second-line therapy and ABA may be a third-line option in monotherapy or in combination with other immunosuppressive therapies (Knobler et al. 2024).

2.2.9.3 Phototherapy

Ultraviolet (UV) phototherapy is another option in the treatment of superficial morphea lesions in adults, as it produces anti-inflammatory and anti-fibrotic effects. Typically, the effect of phototherapy begins after 8-12 weeks after the initiation of treatment. The phototherapy options are psoralen plus UVA (PUVA), UVA1, broadband UVA and narrowband UBV phototherapies (Knobler et al. 2024). The primary option is UVA1, the secondary is PUVA, and the third is UVB.

The patient selection is crucial as phototherapy does not reach the deeper tissues, but the results of efficacy of UVA1 are promising. Phototherapy should be avoided in children (Papara 2023).

2.2.9.4 Other treatments

Topical, immunomodulatory and phototherapy play a role in attenuating the inflammation of the skin and underlying tissues. In addition to these treatments, physiotherapy and plastic surgery are sometimes needed in patients with established sclerosis of the skin. Their role is to improve motion e.g. in the extremities and to target aesthetic problems. Several plastic surgery techniques are available (Yan et al. 2025).

3 Aims

The aim of study was to investigate SSc and LS in Finland, with the following main questions:

1. Has the incidence of systemic sclerosis increased in Finland due to the reformed ACR/EULAR 2013 classification criteria?
2. What is the prognosis of SSc? What are the main causes of death and which factors at the time of diagnosis predict death?
3. What are the clinical features of LS in Southwest Finland? What are the most common concomitant autoimmune diseases, and is the risk of cancer increased? How often do SSc and LS occur simultaneously?

4 Materials and Methods

4.1 Systemic sclerosis

4.1.1 Study population

For the SSc study, the data was collected from two hospital districts in Finland, namely Southwest Finland and Northern Ostrobothnia. Those patients, who were older than 16 years of age and had a diagnostic code of SSc [International Classification of Diseases, 10th revision (ICD-10) codes beginning with M34] appearing at least once in their medical records, were identified from the hospital discharge registers of Turku and Oulu University Hospitals. The recordings were collected from outpatient and inpatient visits during the years 1996 through 2018. All these patient records were reviewed retrospectively, and false diagnoses and typing errors were excluded from the study.

Diagnoses were recategorised and divided into different subtypes of the disease by using ACR/EULAR 2013 criteria and the extent of the skin fibrosis. The subtypes were dcSSc, lcSSc and ssSSc. Early SSc was defined as those with having less than nine diagnostic points.

The clinical data were collected until the end of 2020. A total of 464 patient records were reviewed, 171 from Oulu University Hospital and 293 from Turku University Hospital. The study data were collected and managed using REDCap electronic data capture tools hosted at the University of Turku (Harris et al. 2009; Harris et al. 2019).

4.1.2 Clinical data

For patients fulfilling ACR/EULAR 2013 criteria and those considered as early SSc patients, the clinical manifestations, skin biopsy findings and autoantibody profile at the time of diagnosis were collected. This data included the time of diagnosis, the time of RP initiation and the first non-RP, the first hospital visit, the age at disease onset, as well as the data of smoking habits and gender. For deceased patients, the time, place and clinical data of death was collected.

Using ACR/EULAR 2013 criteria, all patients were assessed whether the criteria were fulfilled. These manifestations included skin thickening either in solely hands or more proximally, the fingertip ulcers of pitting scars, telangiectasiae, NVC abnormalities, PAH, ILD or RP. For autoantibodies, the titre of ANA or other autoantibodies was collected. For SSc-specific autoantibodies, the titres ATA, ACA and anti-RNAPol3 antibodies were collected.

The collected data included SSc-related complications and their onsets. These complications comprised ischaemic (permanent ischaemia, fingertip ulcers, acro-osteolysis or amputation), musculoskeletal (myositis or synovitis), gastrointestinal, renal, pulmonary (ILD), cardiac (perimyocarditis or PAH) and haematological (leukopenia or thrombocytopenia) abnormalities or skin calcification. The basis of each complication was assessed: Thorax X-ray or HRCT for ILD assessment, RHC or ultrasonography for PAH, esophageal manometry for gastrointestinal assessment, X-rays of hands and laboratory test results.

The comorbidities of the study population were collected. Concomitant autoimmune diseases included rheumatic autoimmune diseases and other autoimmune diseases, such as thyroid diseases, type 1 diabetes and PBC. The data of simultaneous cardiovascular disease, osteoporosis, chronic obstructive pulmonary disease, hypertension, type 2 diabetes, sleep apnoea, chronic kidney disease, obesity, depression, fibromyalgia and malignancy were collected. Cardiovascular disease included coronary heart disease, cerebrovascular disease and peripheral arterial disease.

4.1.3 Study I: Incidence of systemic sclerosis

In Study I, changes in the incidence rates in the Finnish population were studied during the years 1999 through 2018. For analysing the incidence of SSc, the mean annual incidence was calculated in 5-year intervals: 1999–2003, 2004–2008, 2009–2013 and 2014–2018. This division was made to decrease the annual variation of the SSc incidence occurring randomly. The annual numbers of inhabitants ≥ 16 years of age living in Southwest Finland and Northern Ostrobothnia were obtained from Statistics Finland. As patients under 16 years of age are followed by pediatric rheumatologists, this cut-off age was selected. The incidence rates were calculated for all those fulfilling ACR/EULAR 2013 criteria, and separately for different subtypes of SSc. The patients with less than nine diagnostic points were considered early SSc and were analysed as a separate group. The same population was evaluated using ACR1980-criteria. The gender distribution, the mean age at diagnosis, autoantibody positivity and examination of nailfold capillaries were analysed in different time periods and for disease subtypes. SSc-specific autoantibodies included ACA-, ATA- and RNAPol3-antibodies. The latest examinations were measured only

at the last few years of the study due to the lack of testing availability. Nailfold capillaries were analysed either with NVC, a magnifying glass or by direct visual inspection. For statistical analyses, two ssSSc patients were included in the group of lcSSc.

4.1.4 Study II: Causes and predictors of death

In Study II, the causes and predictors of death were analysed among Finnish patients with SSc. All patients over 16 years of age fulfilling ACR/EULAR 2013 criteria who had at least one visit during the years 1996–2018 were included in the study. The death certificates that included both primary and imminent causes of death were acquired from Statistics Finland up to August 2021. Death certificates and patient records were reviewed retrospectively and the primary cause of death (main reason leading to death) for each patient was reconsidered. These primary causes of death were divided into the following categories: SSc-related, cardiovascular, malignancies and other causes. SSc-related deaths were divided into groups by organ involvement leading to death. These manifestations were ILD, PAH, GI-tract involvement, SRC, pHI and other SSc-related cause. The survival time – from the date of the clinical diagnosis to death – was calculated separately in groups divided by the primary cause of death.

Independent predictors of death were analysed. The effect of the following variables was analysed: age at disease onset, gender, ILD, PAH, GI tract involvement, disease subtype (lcSSc and dcSSc), telangiectasia, smoking (ever vs. never), skin involvement, digital ulcers, ATA positivity and nailfold capillary abnormalities. For the analysis, two ssSSc patients were added to the group of lcSSc. An ILD diagnosis was made via typical findings in thorax X-rays or HRCT. PAH was diagnosed either via RHC or a clinical examination in combination with ultrasonography. GI tract involvement was defined with unintentional weight loss (at least 10%) and other gastrointestinal findings, such as a watermelon stomach, esophageal dysmotility or pseudo-obstruction. Skin involvement was defined by skin thickening proximal to the metacarpophalangeal joints at the point of the SSc diagnosis.

4.2 Localized scleroderma (Study III)

4.2.1 Study population

All patients, children and adults, with the diagnostic code of localized scleroderma [International Classification of Diseases, 10th revision (ICD-10) codes beginning with L94] that appeared at least once in their medical records from January 1, 2005,

to November 30, 2020, were identified from the hospital discharge register of Turku University Hospital. The annual number of inhabitants during that period was obtained from Statistics Finland. The patient records were reviewed retrospectively and incorrect diagnoses and typing errors were excluded. Using the EDF classification criteria, the diagnoses were divided into five main types and their subtypes. The study data were collected and managed using REDCap electronic data capture tools hosted at the University of Turku (Harris et al. 2009; Harris et al. 2019).

4.2.2 Clinical data

The basic demographic data of all study patients were collected at the end of 2023. The mean annual incidence was calculated in four-year intervals during the years 2005–2020. Moreover, the data of extracutaneous manifestations was collected. The basic demographical data of patients was collected, including age at disease onset, gender distribution, smoking habits and symptoms related to SSc (RP). The results of skin biopsies, autoantibody profiles, *Borrelia burgdorferi* antibodies, concomitant comorbidities and treatments used were collected as well. Of the comorbidities, there was a special interest in autoimmune diseases occurring simultaneously and the risk of malignancies. The cut-off titre of 320 was used to assess ANA antibody positivity. The efficacy of the different treatments was assessed by evaluating the electronical health records and it was based on clinicians´ judgement.

4.3 Statistical methods

4.3.1 Study I: Incidence of systemic sclerosis

In presenting the categorical variables, percentages and frequencies were used. The means and standard deviations were used in presenting continuous variables. In the comparison of the two classification criteria and differences between the age at diagnosis and time periods, one-way analysis of variance (ANOVA) was used in testing. When testing the two classification criteria and whether there was a statistical significance between time periods, comparisons between pairs were made and Dunnett´s correction for p-values was used. Two-way ANOVA was used in the additional analyses using ACR/EULAR 2013 criteria including the diagnosis in the model. When there was a statistically significant interaction of the period and diagnosis, the effect of the period in diagnosis groups was analysed. If the p-value was significant, then other periods were compared to the first one. In correcting p-values, Bonferroni method was used with the results presented in means and 95% confidence intervals (95% CI). Chi-squared test or Fisher´s exact test (in small frequencies) was used in testing the differences between time periods in the

categorical variables. P-values less than 0.05 were considered statistically significant in the two-sided tests used. SAS System for Windows, Version 9.4 (SAS Institute Inc., Cary NC; USA) were used in the statistical analyses.

4.3.2 Study II: Causes and predictors of death

Descripted statistics were used in summarising variables. Chi-square test or Fisher′s exact test were used for analysing associations between death and categorical variables. Fisher′s test was used if the assumptions of chi-square test was violated. One-way ANOVA and the Kruskal-Wallis tests were used in analysing the age at death and the time from diagnosis to death in relation of cause of death. Kaplan-Meier method was used in the survival analyses and multinominal logistic regression analysis was used to analyse independent effect of different explanatory variables between death of all causes. The normality of variables was evaluated by visual evaluation and the Shapiro-Wilk test. Nonparametric methods were used for the non-normality continuous variables. All tests were performed as two-sided with significance level set at 0.05. SAS system, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US) was used in carrying out the analyses.

4.3.3 Study III: Localized scleroderma

Descripted statistics were used in summarising variables, counts and percentages for categorical variables and median and interquartile ranges (IQR) for continuous variables. Kruskal-Wallis test (continuous variables), chi-square or Fisher′s exact test was used in analysing the associations between morphea type and different variables. These tests were used in assessing associations between autoimmune diseases or autoantibodies and different variables. In the analysis of the incidence rates, Kendall′s Tau-b correlation test was used. Visual evaluation was used in assessing the normality of variables and the Shapiro-Wilk test was used. All tests were performed as two-sided with significance level set at 0.05. SAS system, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US) was used in carrying out the analyses.

4.4 Ethical considerations

The studies in this dissertation were retrospective, non-interventional studies without direct patient contacts. No informed patient consents or ethical committee approvals were needed according to Finnish legislation.

For Study I, permissions were acquired from hospital districts of Southwest Finland (T97_2019) and Northern Ostrobothnia (8/2019).

For Study II, permissions were obtained from the Statistics Finland (TK/1655/07.03.00/2021) in addition to permissions from two hospital districts Southwest Finland (T97_2019) and Northern Ostrobothnia (8/2019).

For Study III, permission was acquired from the hospital district of Southwest Finland (T287_2021–1).

The artificial intelligence (AI) tool ChatGPT was used in creating Figures 1 and 3. In addition, ChatGPT was used in the Study III for revising the language during editing the manuscript. The author takes full responsibility for the content.

5 Results

5.1 Study I

5.1.1 Patient population

5.1.1.1 Patients fulfilling ACR/EULAR 2013 criteria

During the years 1999–2018 in both hospital districts, using ACR/EULAR 2013 classification criteria, 246 new patients (84.5%), from 291 with M34 diagnoses, were reclassified as having SSc. Diagnoses were made either at rheumatology outpatient or inpatient visits. At the end of year 2018, there were altogether 743 075 inhabitants in these hospital districts, 419 405 in Southwest Finland and 323 670 in Northern Ostrobothnia. Figure 4 presents the distribution of diagnoses in both hospital districts.

The proportion of the different subtypes of SSc were as follows: 84.1% of patients had lcSSc, 15.0% had dcSSc and 0.8% had ssSSc. Of the 291 patients, 45 patients (36 from Southwest Finland and 9 from northern Ostrobothnia) did not fulfil ACR/EULAR 2013 criteria and they were considered to have early SSc. There was a female preponderance among all SSc patients, 200 of 246 (81.3%) patients. This was even more obvious in the group of lcSSc, with 178 females out of 207 lcSSc patients (86%). In the dcSSc group, 21 (56.8%) of 37 patients were females. Moreover, 36 of 45 (80%) of early SSc patients were female.

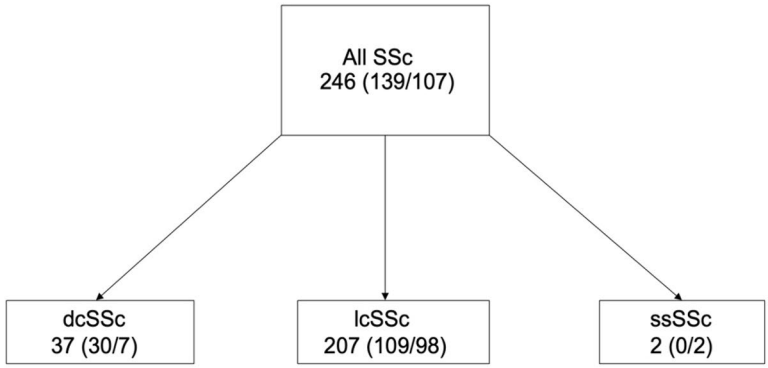

Figure 4. Distribution of different subtypes of systemic sclerosis in two university hospitals. A total number of patients and distribution by hospital districts (Southwest Finland/ Northern Ostrobothnia). SSc; systemic sclerosis, dcSSc; diffuse cutaneous systemic sclerosis, lcSSc; limited cutaneous systemic sclerosis, ssSSc; systemic sclerosis sine scleroderma.

5.1.1.2 Patients fulfilling ACR 1980 criteria

The data for ACR 1980-criteria were available for 268 out of 291 patients. Among the subgroups divided by skin involvement, the data were available for 33, 189 and 2 patients in the dcSSc, lcSSc and ssSSc groups, respectively. Altogether, 70 patients fulfilled ACR 1980 –criteria in the same population. A total of 29 patients were considered to have dcSSc and 41 lcSSc. The majority of the patients fulfilling ACR 1980-criteria were females, 46 out of 70 patients (65.7%). In the group divided by skin involvement, 14 of 29 (48.3%) patients were female in the dcSSc group and 32 of 41 (78.0%) in the lcSSc group.

5.1.2 Age at disease onset

The age at disease onset for patients fulfilling ACR/EULAR criteria was 56 years, which did not change during the study period. Patients with the dcSSc subtype tended to be slightly younger than those with the lcSSc subtype.

5.1.3 Autoantibodies

The frequency of autoantibody positivity did not change during the study period. Of the whole study population, 90.4% were positive for ANA and 84.2% were positive for SSc-specific antibodies. ACA were the most detected SSc-specific autoantibodies (73.3%), 9.4% were positive for ATA, and due to lack of testing availability, only four patients were positive for RNAPol3. ACA were detected as

follows: 100% in ssSSc, 82.2% in early SSc, 81.1% in lcSSc and 10.8% in dcSSc. The distribution of ATA positivity was as follows: 32.4% in dcSSc, 6.3% in lcSSc and none in early SSc or ssSSc.

5.1.4 Nailfold capillary abnormalities

Nailfold capillaries were analysed from 202 patients (69.4%) of the whole study population. No statistically significant difference was shown in the positive findings during the study period. An increasing trend of examination of capillaries was observed during these years. (Figure 5). Patients with early SSc are included in these numbers.

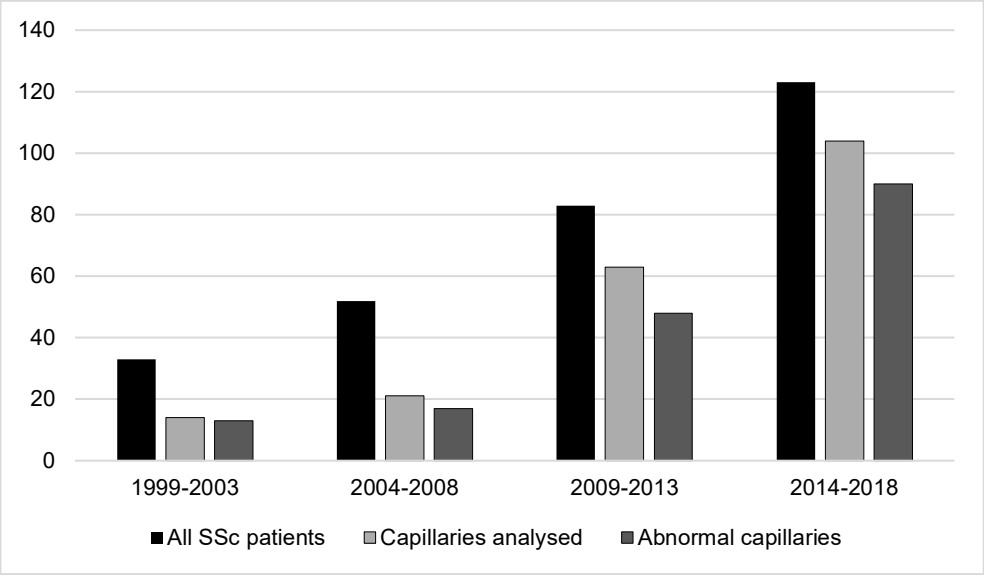

Figure 5. The number of patients with their capillaries analysed and abnormal findings. SSc; systemic sclerosis.

5.1.5 Incidence of systemic sclerosis

5.1.5.1 By subtypes of systemic sclerosis

Figure 6 presents the incidence rates by different subtypes of the disease; cases per million inhabitants. The incidence increased in the lcSSc group, and the increase was statistically significant when the first and second periods were compared to the last one, the result of which is presented in the article of Study I (Table 4).

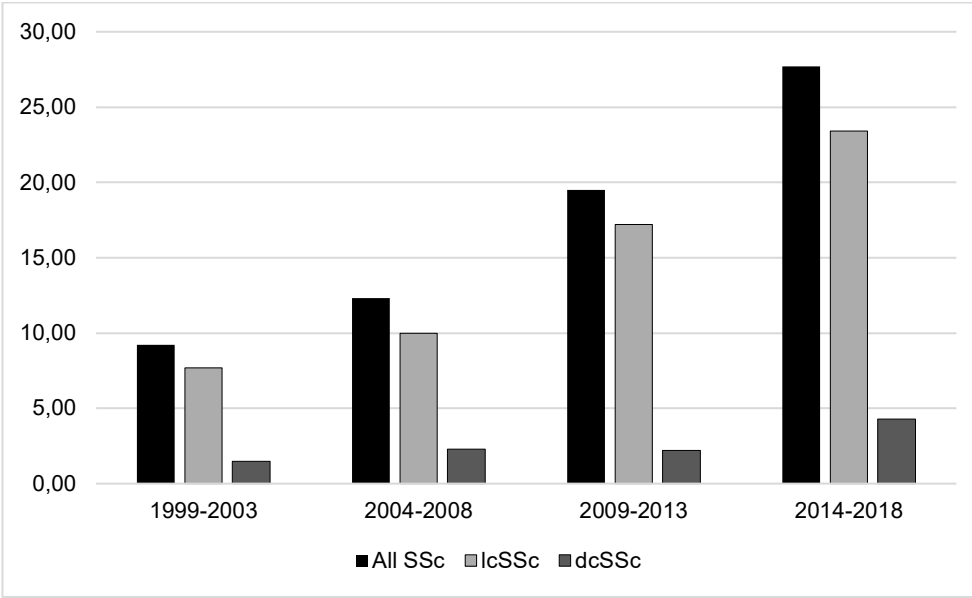

Figure 6. The incidence rates per million inhabitants for all SSc patients and limited (lcSSc) and diffuse cutaneous (dcSSc) subtypes separately. SSc; systemic sclerosis

5.1.5.2 By different classification criteria

Incidence rates by different classification criteria are presented in the Figure 7. The same results are presented in Study I, in Table 4 and Figure 1. The increase was statistically significant when the first and last periods were compared using ACR/EULAR 2013 criteria but not with ACR1980-criteria. Using the latest criteria, the increase was statistically significant in the last two periods compared to the first period.

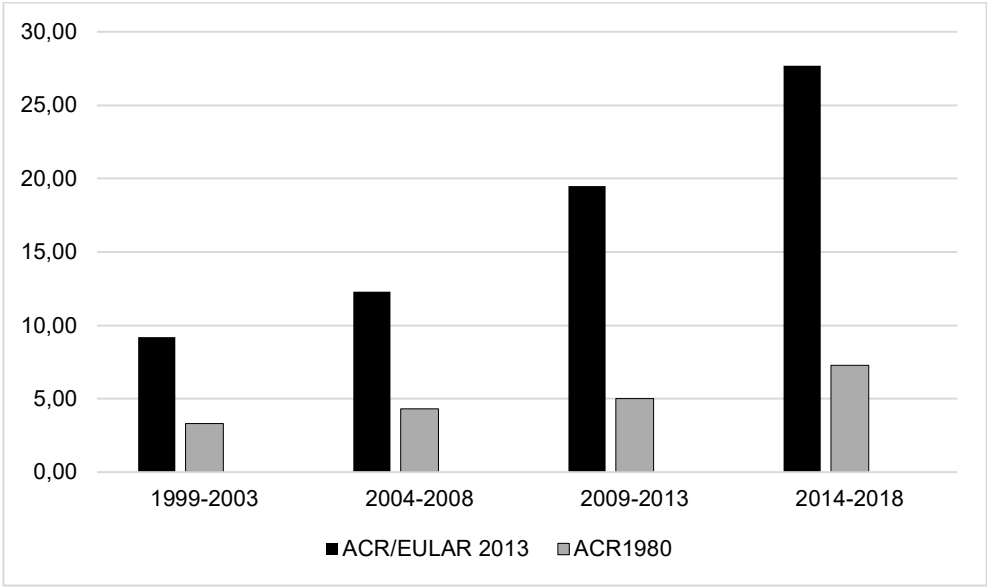

Figure 7. The incidence rate of systemic sclerosis per million inhabitants using ACR/EULAR 2013 and ACR1980 -criteria (Modified from Kortelainen et al. 2024).

5.2 Study II

5.2.1 Clinical data and prognosis

A total of 313 patients fulfilling ACR/EULAR 2013 classification criteria were identified from the patient records. Among this population, 91 deaths occurred between April 2000 and September 2020. For all deceased patients, the subtypes of SSc were divided as follows: 66 (72.5%) had lcSSc, 23 had dcSSc (25.3%) and two (2.2%) had ssSSc.

Figure 8 presents the Kaplan Meier survival curves of all SSc patients with SSc stratified by gender. The overall 5- and 10-year survival rates were 88.4% and 80.2%, respectively. Female patients had a better prognosis, with 5- and 10-year survival rates of 90.1% and 84.4%, compared to 75.2% and 64.0% among male patients, respectively. The difference was statistically significant.

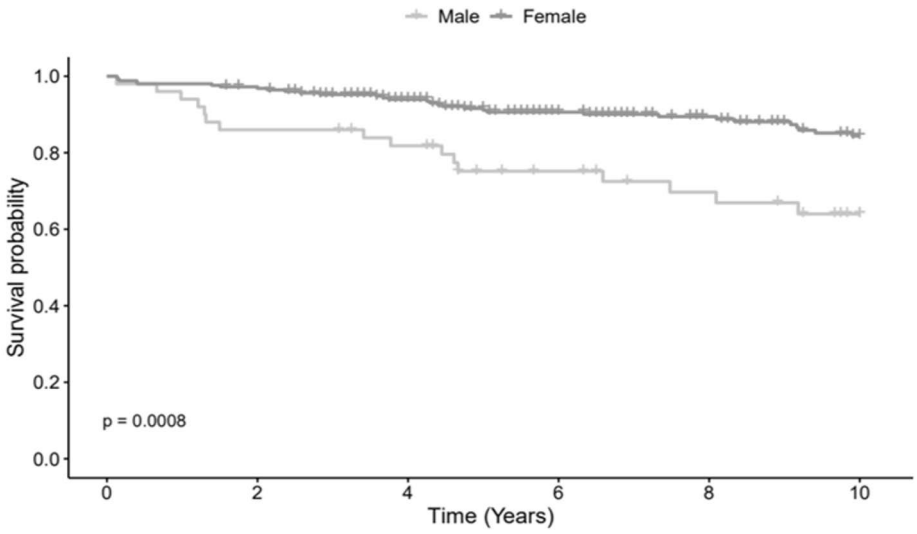

Figure 8. The Kaplan-Meier of 10-year survival rate for female and male patients separately.

5.2.2 Causes of death

The most frequent primary cause of death was SSc-related, accounting for 35 of 91 deaths (38.5%). The proportion of SSc-related deaths differed by disease subtype, occurring in 12 of 23 patients (52.2%) with dcSSc, 22 of 66 patients (33.3%) with lcSSc, and 1 of 2 patients (50%) with ssSSc. Among the 22 patients with lcSSc who died due to SSc, the diagnoses had been made between the years 1982 and 2016. In the dcSSc group, 12 patients died due to SSc, with diagnoses established between 1987 and 2017. For the single patient with ssSSc who died due to SSc, the diagnosis was made in 2006.

ILD either occurring with or without secondary pulmonary hypertension and PAH were the most common SSc-related causes of death with 13 and 11 deaths, respectively. Additionally, one patient had both ILD and PAH equally contributing to the death. Deaths due to ILD occurred both in patients with lcSSc and dcSSc, but deaths due to PAH occurred mainly in the group of lcSSc (10 of 11). In addition, one ssSSc patient died due to PAH. Death due to cardiovascular disease was the second most common primary cause of death with 20 deaths. The types of deaths due to cardiovascular diseases were as follows: coronary heart disease (n=13), peripheral artery disease (n=4), essential hypertension (n=2) and stroke (n=1). All four deaths due to SRC occurred in dcSSc patients.

Deaths due to malignancy occurred in 18 patients, with cancer of the gastrointestinal tract being the most common (n=6). The other cancers leading to death were as follows: lung cancer (n=4), cancer of liver and biliary tract (n=2), lymphoma (n=2), malignant myeloma (n=1) and cancer of unknown origin (n=3).

Other primary causes of deaths were as follows: trauma (n=4), chronic obstructive pulmonary disease (n=3), liver cirrhosis (n=2), Alzheimer′s disease (n=2), septicaemia (n=1), long QT interval (n=1), gut occlusion (n=1), meningioma (n=1), alcohol abuse (n=1), cerebral haemorrhage (n=1) and unknown cause (n=1).

5.2.3 Time from diagnosis to death

Figure 9 presents the median times from the SSc diagnosis to death due to SSc-related and non-SSc-related causes. Deaths due to SSc occurred significantly earlier from the diagnosis compared to those with non-SSc related causes; the median times and IQRs were as follows: 4.4 years [IQR 1.5, 11.8] and 10.8 years [IQR 4.7, 17.1].

Among SSc-related complications, death due to SRC occurred the fastest, as the median time was 0.3 years [IQR 0.1, 0.5] from diagnosis. Median times and IQRs due to other causes were as follows: gastrointestinal (GI) tract involvement 1.5 years [IQR 1.3, 8.1], PAH 3.7 years [IQR 1.5, 4.6], ILD 11.8 years [IQR 4.4, 14.1], pHI 12.2 years [IQR 9.2, 15.3], and other SSc-related causes 12.3 years [IQR 9.9, 14.7].

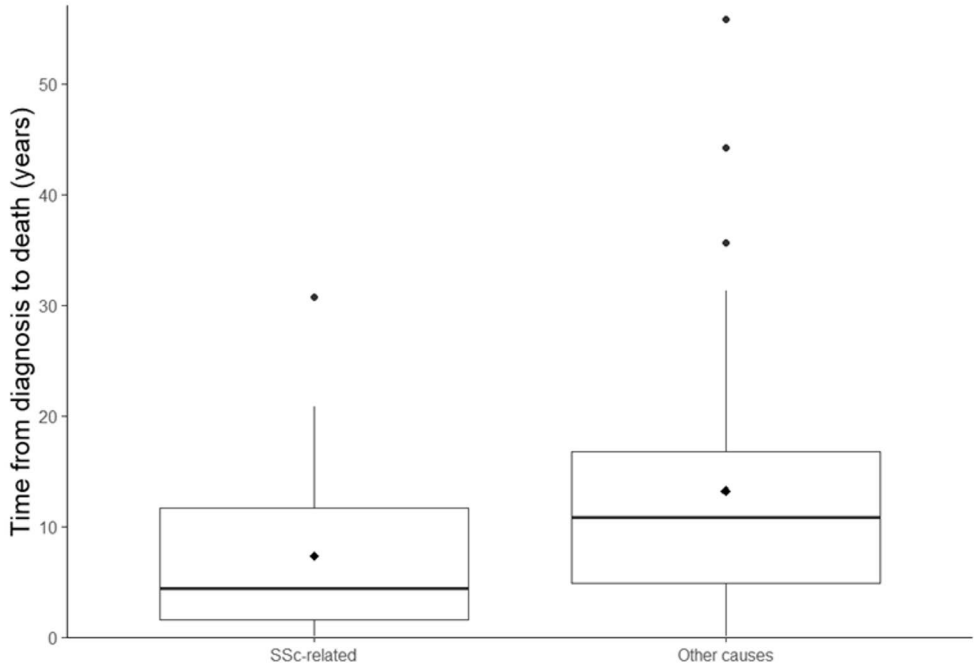

Figure 9. The median times from the SSc diagnosis to death by SSc related causes and other causes of death. SSc; systemic sclerosis. The figure was created by Tiia Rissanen and published with permission.

5.2.4 Age at death

Patients who died due to SSc were significantly younger than those who died due to non-SSc related causes; mean ages ±SD were 65.5 ± 12.7 and 74.2 ± 9.6 years, respectively, as presented in Figure 10. Among SSc-related complications leading to death, patients who died due to GI tract involvement were the youngest; 51 ± 6.7 years. The ages ± SD at death due to other complications were as follows: SRC 62 ± 13.5 years, ILD 62.5 ± 13.4 years, myocardial involvement 69.5 ± 23.3 years, PAH 72.4 ± 5.2 years and other causes 77 ± 14.1 years.

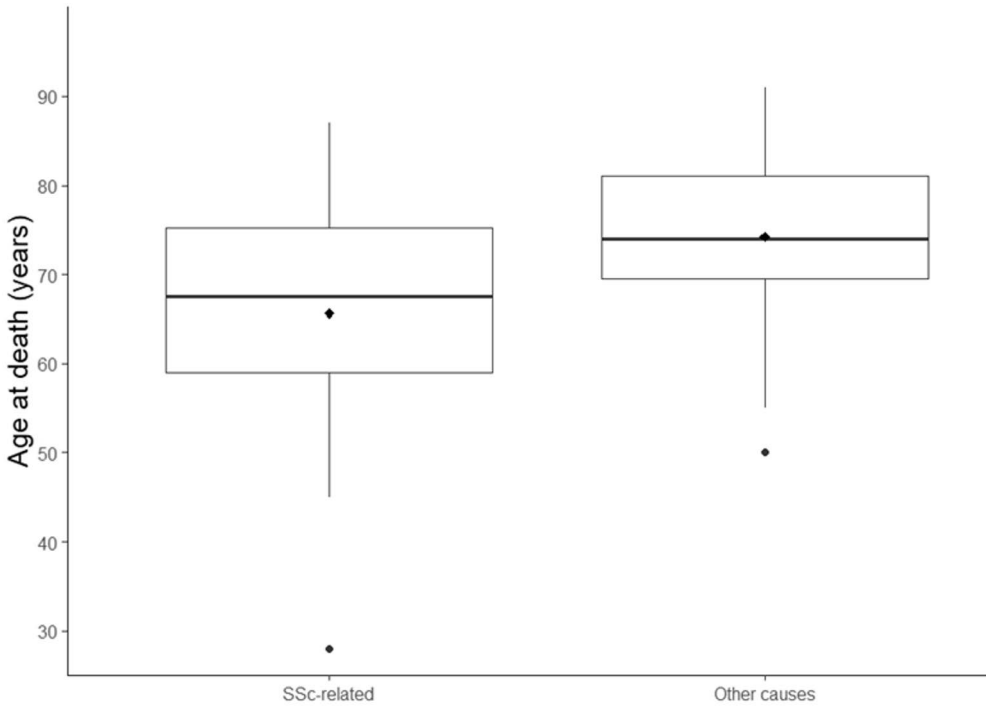

Figure 10. The mean ages at death by SSc related and other causes of death. SSc; systemic sclerosis. The figure was created by Tiia Rissanen and published with permission.

5.2.5 Predictors of death

ILD, PAH, GI-tract involvement, older age at disease onset and male gender were found to be independent risk factors for all causes of death. Nailfold capillary abnormalities were associated with better outcomes.

5.2.6 Autoantibodies

The majority of 91 deceased patients were positive for either ANA or SSc-specific antibodies. Of these, 72 (79.1%) were positive for ANA and 61 (67.0%) were positive for SSc-spesific antibodies. ACA were detected in 49 (53.8%) and ATA in 11 (12.1%) and 1(1.0%) patient was positive for RNAPol3. Among those who died due to SSc-related causes, 18 were positive for ACAs, 5 for ATA, and 1 for RNAPol3 (Figure 11).

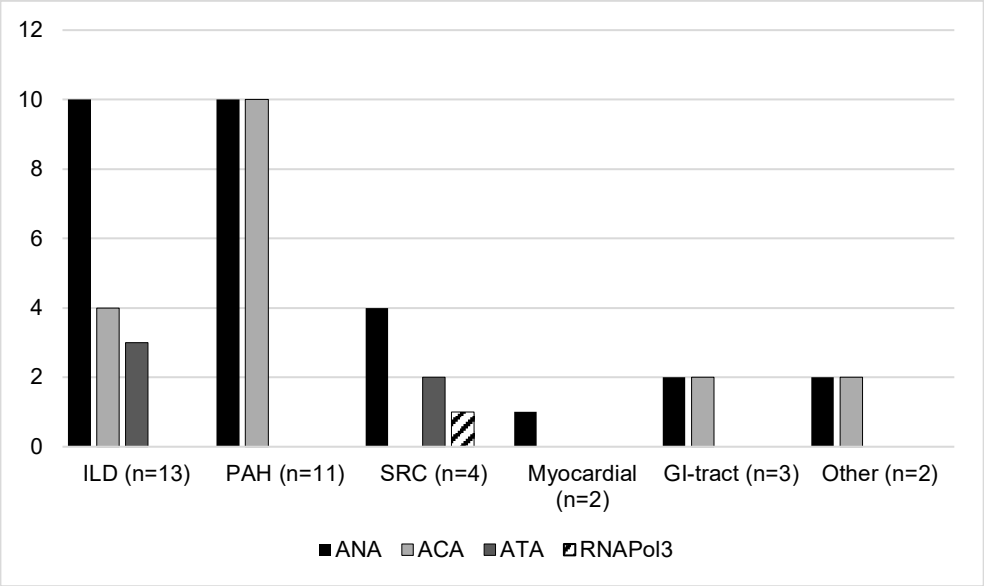

Figure 11. The number of patients positive for different SSc-related autoantibodies by complications leading to death. ACA; anticentromere antibody, ANA; antinuclear antibody, ATA; antitopoisomerase antibody, ILD; interstitial lung disease, PAH; pulmonary arterial hypertension, SRC; scleroderma renal crisis.

5.3 Study III

5.3.1 Basic demography of study patients

Altogether, 155 patients with morphea were identified from the patient records. The majority of patients had limited type with plaque morphea subtype. For pediatric-onset patients, linear type of extremities was the most common subtype. Table 10 presents patients with different main types and their subtypes of morphea. Division was made by age at disease onset (adult vs pediatric). The data of their age at the diagnosis was available for 149 patients.

The incidence had two peaks, one in the childhood and another one in the middle-age. The median ages at the diagnosis were 9.0 years [IQR 5.0, 14.0] for children and 56.5 years [IQR 37.0, 67.0] for adults. Morphea was more common among females (n=125, 80.6%) than males, with a female to male ratio of 4.2:1. These ratios were 4.5:1 and 3.3:1 for adult-onset and pediatric-onset patients, respectively. The mean annual incidence of morphea was 1.62 per 100 000 inhabitants for the study period. The results of skin biopsies were available for 139 patients.

Table 10. The distribution of the different types and subtypes of morphea divided in adult-onset and pediatric-onset patients. The age at the diagnosis was available for 149 patients.

Morphea type and subtype	Adult onset	Pediatric onset
Limited type		
Plaque morphea	61	8
Guttata morphea	1	-
Atr Pasini et Pierini	1	-
Generalised type		
Generalised morphea	51	4
Disabling pansclerotic morphea	1	-
Linear type		
Extremities	1	11
En coup de sabre	3	4
Parry Romberg syndrome	1	-
Deep morphea	2	-

5.3.2 Extracutaneous manifestations

Six patients had extracutaneous manifestations of morphea, all of which were musculoskeletal. The subtypes of morphea of these patients were divided as follows: two had en coup de sabre, one had linear scleroderma of extremities, one had plaque type, one had generalised and one had deep morphea. For five of seven patients with the en coup de sabre type of morphea magnetic resonance imaging (MRI) of the head was performed. Two patients had inflammation in the soft tissue, one also had changes in the fascia, and two had bony lesions. No changes in the brain tissue were observed, and ophthalmological and neurological examinations were normal.

5.3.3 Concomitant autoimmune diseases

A total of 59 autoimmune diseases occurred in 45 (29%) patients simultaneously. These patients were significantly more often females; 43 patients were females and 2 were males. Concomitant autoimmune diseases occurred mainly in adult-onset morphea patients, 42 versus 3 pediatric-onset patients.

The most common autoimmune diseases were thyroid diseases, with 23 cases; of these, 21 had autoimmune thyroiditis and 2 had Graves′ disease. Ten cases of LSA were observed. Nine patients had rheumatoid arthritis and three patients had SSc. All patients with concomitant SSc had a limited subtype (lcSSc). Two cases of psoriasis, lichen planus and vitiligo and one case of alopecia areata, systemic lupus erythematosus (SLE), undifferentiated connective tissue disease (UCTD), SjD, ancylosing spondylitis, coeliac disease, AIH and inflammatory bowel disease were detected.

5.3.4 Malignancies

In 23 patients, 27 malignancies were diagnosed. Of these 23 patients, 19 were females and 4 were males. Malignancies occurred mainly in adult-onset patients, with 22 cases. One cancer was diagnosed in a pediatric-onset patient, adenocarcinoma with probable origin in the pancreas, at the age of 58.

The median age at the cancer diagnosis was 62 years and 1 month [IQR 58.3, 70.9]. Concomitant LSA was associated with an increased risk of malignancy originated from various tissues. Of these patients, four out of ten had additional cancer diagnoses.

A total of 11 cases of breast cancer were diagnosed, and it was the most common cancer type. All were females and the median age at the breast cancer diagnosis was 62 years [IQR 54.3, 67.6]. Seven breast cancer diagnoses were made within four years of the morphea diagnosis, but it was separated from radiation-induced morphea.

5.3.5 Laboratory findings

5.3.5.1 Autoantibodies

The serum autoantibodies related to morphea were analysed for 140 patients and ANA were detected in 44 patients (31.4%) with mostly low titres (640 or below). ANA positivity was significantly more common among pediatric-onset patients than adult-onset ones (48.2% vs 25.4%). Two patients were positive either for AHA- or anti-DNA-antibodies with low titres. In addition, five were positive for anti-SSA/Ro-

antibodies, two for rheumatoid factor or anti-RNP-antibodies. ANCA, ACA, anti-SSB anti-Ku 72/86 or PM-Scl 75 were detected in one patient. Some patients had more than one positive antibody.

5.3.5.2 Borrelia burgdorferi

Three (2.9%) of those analysed for *B.burgdorferi* antibodies (n=103) were positive and for two of them, the titres were low. Only the test for IgM antibodies was positive. The C6-index was not analysed. For two patients, a local cutaneous borrelia infection was excluded by examining the skin biopsy. The other patient was treated with antibiotics before a skin biopsy was taken and PCR was negative. This patient had a high titre of *B.burgdorferi* antibodies, both IgM and IgG, and the C6-index was 8.46. All three patients received antibiotic treatments, and none had treatment response to skin lesions.

5.3.6 Treatments

Morphea patients were treated with topical treatments, systemic immunomodulatory agents, phototherapy or their combinations. The majority (n=136, 87.7%) were treated with topical treatments and high-potency glucocorticoids were the most commonly used (n=122), 57 were treated with topical calcineurin-inhibitors, 11 with calcipotriol and 4 with calcitriol.

The systemic immunomodulatory treatment was used in 41 patients. MTX was the most commonly used (n=25). Other agents were HCQ (n=17), systemic glucocorticoids (n=4,), leflunomide (n=1) and pentoxiphylline (n=1). Two patients received MTX and HCQ in combination and one received multiple immunomodulatory treatments.

Phototherapy was used in 63 patients, with UVA1 being the most commonly used (n=54). Psoralen plus UVA (PUVA) was used in five and UV311 in four patients.

Methotrexate was beneficial for 64% and phototherapy for 77.8% of the treated patients.

6 Discussion

6.1 Epidemiology of systemic sclerosis

Study I provides information on the epidemiology of SSc. The incidence has increased using ACR/EULAR 2013 classification criteria (van den Hoogen et al. 2013), which detect milder cases of SSc and those without skin fibrosis. An increasing trend was observed using ACR 1980-criteria (Masi et al. 1980), though no statistical significance was found. Overall, the awareness of the disease is likely increasing as well.

6.1.1 Incidence by different classification criteria

In a systematic review and meta-analysis (Bairkdar et al. 2021), the methodology of these analysed studies varied in assessing the prevalence and incidence of SSc. A total of 39 studies on incidence were analysed. Only three studies (Andreasson et al. 2014; Elfving et al. 2016; Horimoto et al. 2017) used ACR/EULAR 2013 criteria for analysing the incidence of SSc. The other studies used the older criteria, ICD-codes or a doctor′s opinion on the basis of the diagnoses. The incidence estimates were higher in the latest studies. There are worldwide differences in the incidence of SSc, but variable methodologies make it difficult to compare the results. The incidence seems to be the highest in North America and the lowest in Asia. The data is lacking in some parts of the world, e.g. from Africa.

In Europe, using the older criteria, incidence rates are higher in the southern parts than the northern parts. Andreasson et al. (2014) found the incidence rates to be higher in southern Sweden during the years 2006–2010 even when ACR 1980 criteria were used, compared to older studies. The incidence was higher using ACR/EULAR 2013 criteria. The rates were 14 and 19 per million inhabitants using these two criteria, respectively, which are higher than what has been previously reported in northern Europe (Geirsson et al. 1994). Most likely, knowledge of the disease, in addition to improved diagnostic methods and sensitive classification criteria, has increased. The data is reliable, as all patient records were reviewed by physicians and the diagnoses were confirmed. The majority (82%) of patients had lcSSc. In our study, where the incidence rates were analysed in 5-year periods

between 1999 and 2018, we found that the incidence was similar in the years 2009 through 2013 than what was found in Sweden during nearly the same time period. In the latest period of 2014–2018, the mean annual incidence rate was even higher, 27.7 per million inhabitants. In our study, an increase in the incidence was observed in the lcSSc subtype, supporting the notion that milder cases have been increasingly diagnosed in recent years. We found that the incidence increased only when the latest ACR/EULAR 2013 criteria were used not with the ACR1980-criteria. Therefore, there is therefore no evidence that the disease is becoming more common.

6.1.2 Subtypes of systemic sclerosis

The total proportion of lcSSc patients was 84.5% in our study, which is similar to Sweden and close to what is observed in a Norwegian study, where 244 of 312 (78.2%) SSc patients had a limited cutaneous subtype (Hoffmann-Vold et al. 2013). In southern Europe, the proportion of dcSSc cases has been reported to be higher. In a study conducted utilising the EUSTAR database of incident SSc patients, 35.7% developed a dcSSc subtype within 3 years (Wirz et al. 2016). It is possible that some of the difference is explained by the fact that the EUSTAR database likely does not include all the mildest cases of SSc, which all have lcSSc or ssSSc subtypes.

6.1.3 Nailfold videocapillaroscopy

During the study period, the use of NVC became more common in two clinics, which likely partly increased the incident cases. An abnormal finding in NVC has a significant role in ACR/EULAR 2013 classification criteria, comprising two diagnostic points. The device was acquired at our clinics in the years 2010 and 2012, before these years nailfold capillaries were sometimes analysed by a magnifying glass or direct inspection. In our study, the capillaries were analysed more frequently in the last two study periods than before when the NVC device was available. This likely partially increased the number of new diagnoses, as NVC changes were easier to detect and patients without extensive skin involvement could be diagnosed.

6.2 Clinical course of systemic sclerosis

6.2.1 Survival and prognostic factors

In Study II, the prognosis, causes and predictors of death were analysed over a 20-year period, 2000-2020. Altogether, 91 deaths occurred during the period. The overall 5- and 10 -year survival rates were 88.4% and 80.2%, respectively. The rates were analysed for all SSc patients despite the cutaneous subtype or other known risk

factors. The females had a better prognosis than males. The male gender is a known risk factor for worse survival, which is in line with our results (Elhai et al 2017). The new treatments have only a minor effect on these results, as the majority of the study population were treated with conventional therapies.

The prognostic SCOpE score was proposed by Elhai et al. (2017) from the EUSTAR database of 11 193 SSc patients. Older age, male gender, dcSSc subtype, elevated CRP, class II-III dyspnoea, ILD, low DLCO, low FVC, proteinuria, SRC, impaired left ventricular ejection fraction, DUs and joint involvement were independent predictors of the three-year mortality. The SCOpE score, which ranges between 0 and 32, was developed using these variables. The three-year mortality was higher in the higher scores. The patients in the lowest quarter with less than five points had a 98% 3-year survival whereas those in the highest quarter with 15 or more points had a 53% 3-year survival. Overall, 599 patients had the highest scores, and 2777 patients had the lowest scores. In our study, ILD, PAH, GI tract involvement, male gender and older age were found to be independent predictors of all causes of death. The implementation of this risk score in clinical practice or taking these risk factors in consideration could help to identify the patients at the highest risk. This justifies more frequent follow-up visits and screening of the different organ manifestations for the patients at the highest risk, as more effective treatments are now available for different manifestations. Patients with the lowest risk could have follow-up visits less often, and the resources could be allocated for the most severely ill patients. The national treatment pathway in Finland was established in year 2022 to identify organ manifestations earlier. It is currently available in all clinics to detect patients with the highest risk of mortality and organ failure.

6.2.2 Causes of death

SSc is also a severe disease in Finland, according to our study. The disease itself was the primary cause of death for a significant part of both dcSSc and lcSSc patients; the percentages were 52% and 33%, respectively. The patients who died due to SSc were significantly younger than those who died due to other causes. Despite the fact that the majority of these patients were diagnosed before 2013, a careful evaluation remains warranted. As the treatment options for different disease-related manifestations have been developed, and the use of treatment pathways and international treatment recommendations is justified.

Among 35 SSc-related deaths in our study, the cardiopulmonary causes were the most frequent causes of deaths, with 26 deaths. Altogether, 13 died due to ILD, 11 due to PAH and 2 due to pHI. These findings are similar to the previous findings from the 21st century studies (Elhai et al. 2017; Tyndall et al. 2010). Moreover, Steen et al. (2007) studied changes in the causes of death for SSc patients during the years

1972 through 2002. SRC was the most common SSc-related cause of death in the earlier years and later, the cardiopulmonary causes became the most common causes of death. Our study has been conducted after the introduction of ACEi and SRC as a cause of death was rare. Four patients died due to SRC, and two of them were positive for ATA and one for anti-RNAPol3 antibodies. They all had a dcSSc subtype and the deaths occurred very early in the disease course; the median time from the SSc diagnosis was only four months. According to Hudson et al. (2021), SRC typically occurs at the early stage (course less than 5 years) of the disease. Contemporarily, it affects approximately below 5% of SSc patients. Patients with a dcSSc subtype and especially those with positivity for anti-RNAPol3 antibodies are at a high risk of SRC. African American ethnicity is another risk factor. Frequent (at least two times per week) monitoring of blood pressure is crucial, especially for patients with the highest risk for SRC.

Other common causes of death were cardiovascular disease and malignancies. SSc is a known risk factor for both atherosclerosis and cancer. Especially the risk of peripheral vascular disease was over five-fold in the meta-analysis conducted by Cen et al. (2020). The risk of total cardiovascular disease was over two-fold. Four patients in our study died due to peripheral vascular disease and SSc may have contributed to these deaths. A careful evaluation of traditional cardiovascular risk factors is important for all SSc patients, as the risk of cardiovascular disease is significantly increased.

The risk of cancer, especially lung cancer is increased in SSc patients. ILD is a risk factor for lung cancer. In a meta-analysis involving over 12 000 patients, the lung cancer risk was 2.8-fold in SSc patients, and the risk was 1.5-fold in males compared to females (Peng et al. 2020). In our study, the most common cancer type causing death was the cancer of GI tract, and four deaths due to lung cancer were observed. Three of these patients had underlying ILD and one with adenocarcinoma of the lung was a non-smoker. In a Chinese study of SSc patients with lung cancer (n=12), all were females and non-smokers. Eight patients had underlying ILD (Chen et al. 2020). Anti-RNAPol3-antibodies are a risk factor for cancer, but none of our patients who died due to cancer were positive for these. Typically, malignancies among anti-RNAPol3-positive patients occur within the first years after the SSc diagnosis. While there is no consensus of routine screening of cancer among SSc patients, participation in general cancer screening programs is recommended (Denton et al. 2024).

6.3 Localized scleroderma

6.3.1 Basis of diagnoses

Study III provided information on localized scleroderma ie. morphea patients over a 16-year period, where the majority of diagnoses were biopsy-confirmed. According to the international guidelines, the histopathological confirmation is not mandatory, but it is informative in atypical or unclear presentations (Knobler et al. 2024). As it also provides information about the depth of the inflammation, the biopsy should therefore be sufficiently deep. Only a few patients with morphea, we did not have the histopathology of the skin examined or we did not have the data of it. For the majority of those patients, the diagnosis was evident clinically.

Antibodies against *B. burgdorferi* were frequently analysed, as the geographic location was in an endemic area. Positive findings were rare. The guidelines do not recommend routine screenings of these antibodies (Knobler et al. 2024). Erythema migrans caused by *B. burgdorferi* is the disease that should still be considered in the differential diagnosis of morphea. Around one third of tested patients were positive for ANA, but titres were relatively low. Only one was positive for AHA and one for anti-DNA. The association of these antibodies and disease severity has been observed (Khatri et al. 2019). In a recent German study of morphea patients, around half of the patients were positive for ANA. The cut-off of the ANA titre was 1:80 (Abdusalanova et al. 2025).

6.3.2 Demography

In our study, the distribution of age at the diagnosis, gender and occurrence of different subtypes is similar to what has been published. Only the proportion of generalised morphea was relatively high. Morphea was more common among females, and the incidence had two peaks, one in childhood and another one in the middle-age. The female preponderance was more obvious among adult-onset than pediatric-onset patients. Linear morphea affecting in most patients′ extremities was the most common type among children and limited plaque type among adults. During the study period, no trend of increasing incidence was observed in Finland, which may be due to the relatively short follow-up time.

6.3.3 Extracutaneous manifestations

Extracutaneous manifestations were rare in our study compared to what has been published previously in pediatric patients (Zulian et al. 2005). All six extracutaneous manifestations were musculoskeletal, and four of them occurred in the pediatric-

onset patients. Three of those four patients had linear morphea. There were 30 pediatric patients in our cohort, and the percentage of patients having these musculoskeletal manifestations were 13.3%. Screening with MRI of the affected areas is still important, especially in those with head variants of linear morphea, as the deeper involvement may be asymptomatic and require more aggressive immunosuppressive therapy.

6.3.4 Comorbidity

The occurrence of other autoimmune diseases was relatively common in our study, with the thyroid diseases and autoimmune skin diseases, especially LSA, being the most common types. The percentages of autoimmune diseases were 29%, which is similar or close to the previously published findings (Leitenberger et al. 2009; Abdusalamova et al. 2025). Adult-onset morphea patients seem to have a more pronounced risk for concomitant autoimmune diseases in both studies. Only three patients had SSc and morphea simultaneously, which is reported to be a rare coexistence (Vanhaecke et al. 2020). Even though they share common histopathological features, they are distinct diseases.

Although no sign of an increased risk of malignancy was observed in our study, but we could not verify it due to the absence of data from the background population. Only three patients had malignancy of the skin, which has been reported to be elevated in morphea patients (Boozalis et al. 2019). No melanoma cases occurred in our study.

6.3.5 Treatment

Morphea patients in our centre were treated in accordance with the generally accepted treatment guidelines. The majority of morphea patients were treated with topical treatments, solely or in combination with other treatments. For those patients treated with only topical treatments, the efficacy could not be assessed as they were not followed in our centre. MTX was the most common systemic treatment, and it was beneficial for the majority of treated patients. For adult-onset patients, the doses were relatively low, with a median of 10 mg per week. For pediatric patients, the doses were higher. Doses were adjusted due to tolerability, and many adult-onset patients were elderly. Phototherapy was quite often used, and it was effective in selected patients. New treatments, like MMF or biologics were not administrated to our patients.

6.4 Strengths and limitations

The strength of the current study is the reliability of the data and results from the evaluation of each patient record by a physician in both SSc and morphea patients. Each SSc diagnosis was reclassified and the morphea diagnosis verified by clinical data.

The primary cause of death for every deceased patient was assessed by a physician using patient records and death certificates. For morphea patients, the data including skin histopathology was collected retrospectively. The exact data of the occurrence of co-morbidities, malignancies and autoimmune diseases was available. As the date of diagnoses of malignancies was available for all cases, their relation to morphea diagnosis could be assessed.

This thesis provides information on two relatively rare autoimmune diseases. As geographical differences occur, the reliable data of those diseases is now available in Finland and northern Europe for both diseases. For SSc, there are previous large studies from other Scandinavian countries, but not from Finland. For morphea, this is currently a unique study in northern Europe. A recent German study found similar clinical features among morphea patients (Abdusalamova et al. 2025).

The one limitation of this study was that the recordings were unclear or limited in some of the patients, which led to missing data to some extent. Due to the unclear recordings, the association between SSc and the cause of death could not be verified in a few cases. The extent of skin involvement was available for the classification of patients to different subtypes but mRSS was not assessed routinely for patients. It has a significant prognostic value in SSc patients. We added a cutaneous subtype itself in the multinominal analysis of factors predicting death. Overall, the information on the accuracy of diagnoses in Finland is reliable (Paltta et al. 2023).

Diagnostic methods, e.g. the analysis of different autoantibodies, developed during the study period. Anti-RNAPol3-antibodies are included in ACR/EULAR 2013 classification criteria, and they also have prognostic value in SSc patients. The analysis of these autoantibodies was available only in the last few years of the study. As discussed previously, the data of NVC was available limitedly.

SSc is a known risk factor for cardiovascular disease (Peng et al. 2020) and malignancies (Bonifazi et al. 2013). We could not analyse the effect of SSc among those who died due to cardiovascular disease or cancer. While it is possible that SSc contributed to their deaths, but we could not verify it.

The disease onset was set at the date of clinical diagnosis. RP typically occurs early in the years, or in some patients, decades earlier. The disease onset is usually considered to be either the onset of the first non-RP or RP symptom. We had very limited data on the onset of these symptoms.

Another limitation in the studies of both SSc and morphea was that we did not have the data of the background population. We were unable to assess the mortality

risk for SSc patients. It would be interesting to calculate SMRs for Finnish SSc patients as there are differences, depending on the area and the time worldwide. Among morphea patients in our study, cases of malignancies and other autoimmune diseases occurred. We were unable to analyse the risk of cancer compared to the background population due to the lack of data.

The treatment options and screening of different organ manifestations in SSc patients have been developed in recent years. In our study, the effect of either the screening or the modern treatments could not be assessed, as they were provided only in the last few years of the study. The material is thus historical and gives information on the natural course of the SSc in some parts. Treatment options for morphea have increased as well, and this study could not assess their efficacy.

6.5 Future aspects

Despite the large heterogeneity of clinical manifestations of SSc, advances in understanding the early pathogenesis of SSc have been made in the past five years. These methods include single-cell RNA sequencing, next-generation sequencing, genomics, proteomics, metabolomics, spatial biology and microbiome profiling. New technology and artificial intelligence provide opportunities for analysing larger amounts of data and may lead to a more personalised treatment approach (Abraham et al. 2025). The gut microbiome has been noted to be altered at the very early stage of SSc, and its potential contribution to the progression of SSc may lead the gut microbiome to be one of the treatment targets (Bellando-Randone et al. 2024).

There has been a vast progress in the development of treatments to SSc as the knowledge of the disease has increased. However, effective treatments are needed. The mortality is still high compared to background population; it has not decreased as in patients with rheumatoid arthritis.

Different autoantibodies are added to classify the disease and its prognosis (Nihtyanova et al. 2020). More information on their implication of the prognosis, different organ manifestations and co-morbidities is now available. Possibilities to analyse autoantibodies have increased in our centres over the last decade. In the future, their significance could also be assessed in Finland. The implementation of the treatment pathway of the daily practice has led to the screening of different organ manifestations. These manifestations can be detected earlier, and the disease course could possibly be altered. In the future, as the modern treatments are used in everyday clinical practice, the survival of patients could possibly increase. For instance, ILD is a potentially lethal complication in which effective treatments have become available. The different demographical factors and biomarkers may predict treatment responses to different drugs, e.g. tocilizumab in ILD (Ghuman et al. 2024). Among the drugs that are already available, promising results have been obtained

with drugs like abatacept, lenabasum, lanifibranor, romilkimab, ziritaxestat and asengeprat (Abraham et al. 2025).

The Phase II or IIb trials of emerging therapies include CAR-T19, anifrolumab, belimumab, MT-7117, FcRn inhibitors, nerandomilast, amlitelimab, avenciguat, telitacicept and bispesific antibodies activating T cell driven B cell depletion (Santos et al. 2025). Type I interferon (IFN) receptor blocker anifrolumab has been approved in the treatment of SLE. Phosphodiesterase 4B inhibitor nerandomilast has shown efficacy in idiopathic pulmonary fibrosis in the FIBRONEER-ILD study (Maher et al. 2025). Regarding CAR-T19 therapy, which has shown promising results, other cell-based therapies are under investigation (Abraham et al. 2025).

The data on the efficacy of new treatments in morphea is increasing. The knowledge of the increased risk of concomitant autoimmune diseases will guide us to follow these patients more closely and pay attention to symptoms that may indicate the presence of other autoimmune diseases. A recent study suggested the immunoproteasome to be a possible new therapeutic target in morphea (Mähönen et al. 2024). In addition, promising results have been achieved to confirm, e.g. transforming growth factor ß pathway as a treatment target (Mähönen et al. 2025).

Possibly new biomarkers, autoantibodies and clinical characteristics would guide our treatment decisions more in the future, both in morphea and SSc patients.

7 Summary

This dissertation provides the real-life data of two relatively rare autoimmune diseases, which partially share the same pathogenic pathway. In both diseases, the result is excess fibrosis of the skin. In SSc, internal organ involvement is common, and localized scleroderma is limited to skin and sometimes underlying tissues. As more treatments have become available, targeting vasculopathy, inflammation and fibrosis, it is crucial to target an earlier diagnosis and detect disease-related organ complications. Awareness and the development of new effective treatments have led to the development of treatment pathways and international recommendations for these both rare diseases. Our study confirms that the coexistence of these diseases is rare.

Acknowledgements

This study was carried out at the Centre for Rheumatology and Clinical Immunology, which is currently part of the Department of Rheumatology, Turku University Hospital and the University of Turku. Financial support was provided by the Finnish Foundation for Rheumatic Diseases, the Turunmaa Duodecim Society, the Turku University Hospital Education and Research Foundation, Finnish governmental VTR funding, and the Doctoral Programme in Clinical Research of the University of Turku Graduate School.

First of all, I would like to express my deepest gratitude to all my supervisors: Adjunct Professor Laura Pirilä, Adjunct Professor Johanna Huhtakangas, and Professor Veli-Matti Kähäri. Despite your busy schedules, you always found time to answer my questions. Without your continuous support, this work would not have been possible. Laura, I admire your inspiring attitude and the tremendous effort you have invested in advancing science. You have created a unit with extensive expertise in rheumatic diseases and an inspiring atmosphere, which has encouraged many colleagues to work in our department. Johanna, I am deeply grateful for your warm, calm, and wise approach to supervision. Thanks to you, the entire systemic sclerosis project was launched. Veli-Matti, I greatly appreciate your outstanding scientific expertise. I have learned a great deal from you about both science and dermatology.

I am grateful to Adjunct Professor Jaana Panelius and MD Ritva Peltomaa for reviewing this dissertation. I greatly appreciate your valuable advice on improving my work. I also acknowledge MD Laura Kuusalo, MD Ritva Peltomaa, and Adjunct Professor Antti Palomäki for their valuable contributions as members of my doctoral follow-up group.

I wish to warmly thank the statisticians Saija Hurme and Tiia Rissanen for contributing their enormous work to this study. I also thank my co-authors Niina Hieta, Markus Käyrä, Johanna Paltta, and Kirsi Taimen for their valuable contributions to this thesis.

My sincere thanks go to my colleagues in the Department of Rheumatology: Antti Hurme, Ilpo Koskivirta, Taina Kotijärvi, Dimitri Krasnov, Petri Kresanov, Laura Kuusalo, Reetta Laiho, Kaisa Liuhto, Krista Lundelin, Markku Mali, Noora Mattsson, Antti Palomäki, Johanna Paltta, Maija Puurtinen-Vilkki, Kira Rintala,

Laura Ryyppö, Milja Söderström, and Kirsi Taimen. I also warmly thank the entire staff of the Department of Rheumatology. In particular, I am grateful to Katri-Anna Lehto for her invaluable assistance with technical matters.

I would also like to thank my colleague Päivi Ekman for inspiring discussions and practical advice in science, as well as the entire staff of the Department of Rheumatology at Satakunta Central Hospital. I am extremely grateful to Professor Timo Möttönen, Adjunct Professor Oili Kaipiainen-Seppänen, and Adjunct Professor Riitta Luosujärvi for their tremendous support during my early career.

I am especially grateful to my parents, Leila and Risto, for their love and unwavering support throughout my life. You have always encouraged me to pursue education and follow my dreams. I am also grateful to my dear siblings, Laura and Sakari, and their families, for growing up together and always being an important part of my life.

Finally, I wish to thank my family: my beloved husband Ilkka for his endless love, support, and companionship, and my dear adult children Emilia, Kalle, and Vilma, as well as my adorable granddaughter Nella. I feel privileged to have you all in my life. Thank you for being exactly who you are.

Turku, April 2026
Saara Kortelainen

References

Abdusalamova K, Kinberger M, Globig P, Worm M. 2025. Clinical features and treatment of morphea patients: a retrospective analysis. *Eur J Dermatol.* 35(4), p. 294–9.

Abraham D, Black C, Denton C, Distler J, Domsic R, Feghali-Bostwick C. et al. 2025. An international perspective on the future of systemic sclerosis research. *Nat Rev Rheumatol.* 21(3), p. 174–87.

Agarwal S, Tan F, Arnett F. 2008. Genetics and genomic studies in scleroderma (systemic sclerosis). *Rheum Dis Clin N Am*. 34: p. 17–40.

Andreasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. 2014. Prevalence and incidence of systemic sclerosis in southern Sweden: Population-bsed data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. *Ann Rheum Dis.* 73(10), p. 1788–92.

Antoniou K, Distler O, Gheorghiu A-M, Moor C, Vikse J, Bizymi N et al. 2025. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR) Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG). *Ann Rheum Dis.* 00:1–39

Arias-Nuñez M, Llorca J, Vazquez-Rodriguez T, Gomez-Acebo I, Miranda-Filloy J, Martin J et al. 2008. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Medicine.* 87(5), p. 272–80.

Arnett F, Cho M, Chatterjee S, Aguilar M, Reveille J, Mayes M. 2001. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. *Arthritis Rheum.* 44(6), p. 1359–62.

Arthur M, Fett N, Latour E, Jacobe H, Kunzler E, Florez-Pollack S et al. 2020. Evaluation of the effectiveness and tolerability of mycophenolate mofetil and mycophenolic acid for the treatment of morphea. *JAMA Dermatol*. 156(5), p. 521–8.

Asano Y. 2020. The pathogenesis of systemic sclerosis: An understanding based on a common pathologic cascade across multiple organs and additional organ-spesific pathologies. *J Clin Med.* 9(9), p. 1–27.

Auth J, Müller F, Völkl S, Bayerl N, Distler J, Tur C et al. 2024. CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: a case series. *Lancet rheumatol*. 7, p. e83–93.

Avanoglu-Guler A, Campochiaro C, De Luca G, Hughes M, Tufan A, Green L et al. 2024.Calcinosis in systemic sclerosis: an update on pathogenesis, related complications, and management: a heavy burden still waiting to be lifted off patients′ hands. *Semin Arhritis Rheum.* 66: 152431.

Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. 2011. Preliminary criteria for the very early diagnosis of systemic sclerosis: Results of a Delphi consensus study from EULAR scleroderma trials and research group. *Ann Rheum Dis*. 70(3), p. 476–81.

Bairkdar M, Chen E, Dickman P, Hesselstrand R, Westerlind H, Holmqvist M. 2023. Survival in Swedish patients with systemic sclerosis: a nationwide population-based matched cohort study. *Rheumatology*. 62(3), p. 1170–8.

Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema E, Holmqvist M. 2021. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. *Rheumatology*. 60(7), p. 3121–33.

Batani V, Dagna L, De Luca G 2024. Therapeutic strategies for primary heart involvement in systemic sclerosis. *Rheumatol Immunol Res.* 5(2), p. 72–82.

Bellando-Randone S, Del Galdo F, Lepri G, Minier T, Huscher D, Furst DE. 2021. Progression of patients with Raynaud′s phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for the very early diagnosis of systemic sclerosis (VEDOSS*). Lancet Rheumatol*. 3: e834–43.

Bellando-Randone S, Russo E, Di Gloria L, Lepri G, Baldi S, Fioretto B et al. 2024. Gut microbiota in very early systemic sclerosis: the first case-control taxonomic and functional characterisation highlighting an altered butyric acid profile. *RMD Open.* 10(4), e004647.

Bissel LA, Anderson M, Burgess M, Chakravarty K, Coghlan G, Dumitru R et al. 2017. Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. *Rheumatology.* 56(6), p. 912–21.

Bonifazi M, Tramacere I, Pomponio G, Gabrielli B, Avvedimento E, La Vecchia C et al. 2013. Systemic sclerosis (scleroderma) and cancer risk: systematic review and meta-analysis of observational studies. *Rheumatology*. 52(1), p. 143–54.

Boozalis E, Shah A, Wigley F, Kang S, Kwatra S. 2019. Morphea and systemic sclerosis are associated with an increased risk for melanoma and nonmelanoma skin cancer. *J Am Acad Dermatol*. 80(5), p. 1449–51.

Bruni C, Buch M, Djokovic A, De Luca G, Dumitru R, Giollo A et al. 2023. Consensus on the assessment of systemic sclerosis–associated primary heart involvement: World Scleroderma Foundation/Heart Failure Association guidance on screening, diagnosis, and follow-up assessment. *JSRD.* 8(3), p. 169–82.

Bruni C, Guiducci S, Bellando-Randone S, Lepri G, Braschi F, Fiori G et al. 2015. Digital ulcers as a sentinel sign for early internal organ involvement in very early systemic sclerosis. *Rheumatology.* 54(1), p. 72–6.

Bruni C, Ross L. 2021. Cardiac involvement in systemic sclerosis: Getting to the heart of the matter. *Best Pract Res Clin Rheumatol.* 35(3), 101668.

Burt R, Shah S, Dill K, Grant T, Gheorghiade M, Schroeder J. 2011. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with the pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet.* 378(9790), p. 498–506.

Castellvi I, Simeon C, Sarmiento M, Casademont J, Corominas H, Fonollosa V. 2020. Effect of bosentan in pulmonary hypertension development in systemic sclerosis patients with digital ulcers. *PLoS One.* 15(12): e0243651

Cen X, Feng S, Wei S, Yan L, Sun L. 2020. Systemic sclerosis and risk of cardiovascular disease A PRISMA-compliant systemic review and meta-analysis of cohort studies. *Medicine.* 99(47).

Chan E. 2022. Anti-Ro52 Autoantibody is common in systemic autoimmune rheumatic diseases and correlating with worse outcome when associated with interstitial lung disease in systemic sclerosis and autoimmune myositis. *Clin Rev Allergy Immunol.* 63(2), p. 178–93.

Chen M, Liu X, Xu Y, Zhou Q, Shi Y, Zhang D et al. 2020. Clinicopathological characteristics of lung cancer in patients with systemic sclerosis. *Clin Respir J.* 14(12), 1131–6.

Chiu Y, Vora S, Kwon E-K, Maheshwari M. 2012. A Significant proportion of children with morphea En Coup De Sabre and Parry-Romberg Syndrome have neuroimaging findings. *Pediatric Dermatology*. 29(6), p. 738–48.

Christmann R, Wells A, Capelozzi V, Silver R. 2010. Gastroesophageal reflux incites interstitial lung disease in systemic sclerosis: clinical, radiologic, histopathologic, and treatment evidence. *Semin Arthritis Rheum.* 40(3), p. 241–9.

Coghlan J, Denton C, Grünig E, Bonderman D, Distler O, Khanna D. et al. 2014. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 73(7), p. 1340–9.

Coghlan J, Wolf M, Distler O, Denton C, Doelberg M, Harutyunova S et al. 2018. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. *Eur Respir J.* 51(4), 1701197.

Cole A, Ong V, Denton C. 2023. Renal disease and systemic sclerosis: an update on scleroderma renal crisis. *Clin Rev Allergy Immunol.* 64(3), p. 378–91

Cutolo M, Pizzorni C, Tuccio M, Burroni A, Craviotto C, Basso M et al. 2004. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. *Rheumatology*. 43(6), p. 719–26.

Cutolo M, Sulli A, Pizzorni C, Accardo S. 2000. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *J Rheumatol*. 27(1), p. 155–60.

Davuluri S, Lood C, Chung L. 2023. Calcinosis in systemic sclerosis. *Curr Opin Rheumatol.* 36(5), p. 360–9.

Del Galdo F, Lescoat A, Conaghan P, Bertoldo E, Colic J, Santiago T et al. 2025. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. *Ann Rheum Dis.* 84(1), p. 29–40.

De Luca G, Matucci-Cerinic M, Mavrogeni S. 2024. Diagnosis and management of primary heart involvement in systemic sclerosis. *Curr Opin Rheumtol.* 36(1), p. 76–93.

Denton C, De Lorenzis E, Roblin E, Goldman N, Alcacer-Pitarch B, Blamont E. 2024. The 2024 British Society for Rheumatology guideline for management of systemic sclerosis. *Rheumatology*. 63, p. 2956–75.

Denton C, Khanna D. 2017. Systemic sclerosis. *The Lancet,* 390(10103), p. 1685–99

Diab S, Dostrovsky N, Hudson M, Tatibouet S, Fritzler M, Baron M et al. 2014 Systemic sclerosis sine scleroderma: A multicenter study of 1417 subjects. *J Rheumatol.* 41(11), p. 2179–85.

Distler O, Assassi S, Cottin V, Cutolo M, Danoff S, Denton C et al. 2020. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J.* 55: 1902026.

Distler O, Highland K, Gahlemann M, Azuma A, Fischer A, Mayes M et al. 2019. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med.* 380(26), p. 2518–28.

Distler O, Ofner C, Huscher D, Jordan S, Ulrich S, Stähler G et al. 2024. Treatment strategies and survival of patients with connective tissue disease and pulmonary arterial hypertension: a COMPERA analysis. *Rheumatology*. 63(4), p. 1139–46.

Domsic R, Rodriguez-Reyna T, Lucas M, Fertig N, Medsger T. 2011. Skin thickness progression rate: A predictor of mortality and early internal organ involvement in diffuse scleroderma. *Ann Rheum Dis.* 70(1), p. 104–9.

Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y et al. 2021. Safety and efficacyof rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. *Lancet Rheumatol*. 3(7), p. e489–e497.

Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y et al. 2022. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): open-label extension of a double-blind, investigator-initiated, randomised, placebo-controlled trial. *Lancet Rheumatol*. 4(8), p. e546–e555.

Elfving P, Marjoniemi O, Niinisalo H, Kononoff A, Arstila L, Savolainen E et al. 2016. Estimating the incidence of connective tissue diseases and vasculitides in a defined population in Northern Savo area in 2010. *Rheumatol Int.* 36(7), p. 917–24.

Elhai M, Avouac J, Kahan A, Allanore Y. 2013. Systemic sclerosis at the crossroad of polyautoimmunity. *Autoimmun Rev.*12(11), p. 1052–57.

Elhai M, Boubaya M, Distler O, Smith V, Matucci-Cerinic M, Sancho J. 2019. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practise: a prospective cohort study. *Ann Rheum Dis*. 78(7), p. 979–87.

Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. 2012. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology*. 51(6), p. 1017–26.

Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A et al. 2017. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis.* 76(11), p. 1897–905.

Elhai M, Sritharan N, Boubaya M, Balbir-Gurman A, Siegert E, Hachulla E, et al. 2022. Stratification in systemic sclerosis according to autoantibody status versus skin involvement: a study of the prospective EUSTAR cohort. *Lancet Rheumatol.* 4(11):e785–e794.

Eyraud A, Scouppe L, Barnetche T, Forcade E, Lazaro E, Duffau P et al. 2018. Efficacy and safety of autologous haematopoietic stem cell transplantation in systemic sclerosis: a systematic review of the literature. *Br J Dermatol.* 178(3), p. 650–8.

Fan W, Obiakor B, Jacobsson R, Haemel A, Gandelman J. 2023. Clinical and therapeutic course in head variants of linear morphea in adults: a retrospective review. *Arch Dermatol Res.* 315(5), p. 1161–70.

Fan Y, Bender S, Shi W, Zoz D. 2020. Incidence and prevalence of systemic sclerosis and systemic sclerosis with interstitial lung disease in the United States. *J Manag Care Spec Pharm.* 26(12), p. 1539–47.

Ferlito A, Campochiaro C, Tomelleri A, Dagna L, De Luca G. 2022. Primary heart involvement in systemic sclerosis, from conventional to innovative targeted therapeutic strategies. *JSRD*. 7(3), p. 179–88.

Fett N, Werth V. 2011. Update on morphea. Part I. Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol*. 64(2), p. 217–28.

Fichel F, Baudot N, Gaitz J-P, Trad S, Barbe C, Frances C et al. 2014. Systemic sclerosis with normal or nonspesific nailfold capillaroscopy. *Dermatology*.228(4), p. 360–7.

Flavahan NA. 2021. New mechanism-based approaches to treating and evaluating the vasculopathy of scleroderma. *Curr Opin Rheumatol.* 33(6) p. 471–9.

Florez-Pollack S, Kunzler E, Jacobe H. 2018. Morphea: Current concepts. *Clin Dermatol*. 36(4), p. 475–86.

Forbes A, Marie I, 2009. Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. *Rheumatology.* 48, iii36-iii39

Furst D, Fernandez A, Iorga S, Greth W, Bancroft T. 2012. Epidemiology of systemic sclerosis in a large US managed care population. *J Rheumatol.* 39(4), p. 784–6.

Gatta L, Scarpignato C. 2017. Systematic review with meta-analysis: rifaximin is effectiveand safe for the treatment of small intestine bacterial overgrowth. *Aliment Pharmacol Ther*. 45(5), p. 604–16.

Geirsson AJ, Steinsson K, Guthmundsson S, Sigurthsson V. 1994. Systemic sclerosis in Iceland. A nationwide epidemiological study. *Ann Rheum Dis.*53(8), p. 502–5.

Gelber AC, Pillemer SR, Baum BJ, Wigley FM, Hummers LK, Morris S, et al. 2006. Distinct recognition of antibodies to centromere proteins in primary Sjogren′s syndrome compared with limited scleroderma. *Ann Rheum Dis*. 65, p. 1028–32.

Ghuman A, Khanna D, Lin C, Furst D, Raghu G, Martinez F et al. 2024. Prognostic and predictive markers of systemic sclerosis-associated interstitial lung disease in a clinical trial and long-term observational cohort. *Rheumatology*. 63(2), p. 472–81.

Giuggioli D, Colaci M, Cocchiara E, Spinella A, Lumetti F, Ferri C. 2018. From Localized Scleroderma to Systemic Sclerosis: Coexistence or Possible Evolution. *Dermat Res Pract.* 1285687.

Goldman N, Nihtyanova S, Beesley C, Wells A, Denton C, Renzoni E et al. 2025. Tocilizumab and rituximab for systemic sclerosis interstitial lung disease: a real-world cohort analysis. *Rheumatology*. 0, p.1–6.

Goswami R, Ray A, Chatterjee M, Mukherjee A, Sircar G, Ghosh P. 2021. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. *Rheumatology.* 60(2), p. 557–67.

Gumkowska-Stroka O, Kotyla K, Kotyla P. 2024. Immunogenetics of systemic sclerosis. *Genes*. 15, 586.

Haque A, Kiely D, Kovacs G, Thompson R, Condliffe R. 2021. Pulmonary hypertension phenotypes in patients with systemic sclerosis. *Eur Resp Rev*. 30(161) 210053

Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O'Neal L et al. 2019. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform.* 95: 103208.

Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. 2009. Research electronic data capture (REDCap)--a metadata-driven methodology and worflow process for providing translational research informatics support. *J Biomed Inform.* 42(2), p. 377–81

Haussmann A, McMahan Z, Volkmann E. 2024. Understanding the gastrointestinal microbiome in systemic sclerosis: Methodological advancements and emerging research. *Curr Opin Rheumatol.* 36, p.401–9.

Henes J, Oliveira M, Labopin M, Badoglio M, Scherer H, Del Papa N et al. 2021. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party. *Haematologica.* 106(2), p. 375–83.

Herrick A, Wigley F. 2020. Raynaud's phenomenon. *Best Pract Res Clin Rheumatol.* 34, 101474

Hieta N, Rintala M, Söderlund J, Kurki S, Hietanen S. 2021. Comorbidity of Dermal and Cardiovascular Disorders with Lichen Sclerosus: A Case-control Study. *Acta DV.* 101(11): adv00594.

Highland K, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A et al. 2021 Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med* 9(1), p.96–106.

Hoa S, Lazizi S, Baron M, Wang M, Frizler M, Hudson M et al. 2022. Association between autoantibodies in systemic sclerosis and cancer in a national registry. *Rheumatology.* 61(7), p. 2905–14.

Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airo P, Ananieva L et al. 2021. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis*. 80(2), p. 219–27.

Hoffmann-Vold AM, Fretheim H, Midtvedt Ø, Kilian K, Angelshaug M, Chaudhary A et al. 2018. Frequencies of borderline pulmonary hypertension before and after the DETECT algorithm: results from a prospective systemic sclerosis cohort. *Rheumatology*. 57(3), p. 480–7.

Hoffmann-Vold AM, Maher T, Philpot E, Ashrafzadeh A, Barake R, Barsotti S et al. 2020. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statement. *Lancet Rheumatol.* 2(2), p. e71–e83.

Hoffmann-Vold AM, Molberg O, Midtvedt O, Garen T, Gran J. 2013. Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis. *J Rheumatol.* 40(7), p. 1127–33.

Horimoto A, Matos E, da Costa M, Takahashi F, Rezende M, Kanomata L. et al. 2017. Incidence and prevalence of systemic sclerosis in Campo Grande, State of Mato Grosso do Sul, Brazil. *Rev Bras Reumatol Engl Ed.* 57(2), 107–14.

Hudson M, Baron M, Tatibouet S, Furst D, Khanna D, International Scleroderma Renal Crisis Study Investigators.2014. Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis—Results from the International Scleroderma Renal Crisis Survey. *Semin Arthritis Rheum.* 43(5), p. 666–72.

Hudson M, Ghossein C, Steen V. 2021. Scleroderma renal crisis. *Presse Med.* 50(1), 104063.

Hughes M, Heal C, Henes J, Balbir-Gurman A, Distler J, Airò P et al. 2022. Digital pitting scars are associated with a severe disease course and death in systemic sclerosis: a study from the EUSTAR cohort. *Rheumatology*. 61(3), p. 1141–7.

Hughes M, Herrick A. 2017. Digital ulcers in systemic sclerosis. *Rheumatology*. 56(1), p. 14–25.

Hughes M, Pauling J, Armstrong-James L, Denton C, Galdas P, Flurey C. 2020. Gender-related differencies in systemic sclerosis. *Autoimmun Rev.* 19(4), 102494.

Humbert M, Kovacs G, Hoeper M, Badagliacca R, Berger R, Brida M et al. 2022. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 43(38), p. 3618–731.

Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D et al. 2011. Screening for Pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheumatol.* 63(11), p. 3522–30.

Johnson S, Bernstein E, Bolster M, Chung J, Danoff S, George M et al. 2024. 2023 American College of Rheumatology (ACR)/ American College of Chest Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol.* 76(8), p. 1182–200.

Joy G, Arbiv O, Wong C, Lok S, Adderley N, Dobosz K et al. 2023. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. *Eur Respir Rev.* 32: 220210.

Kaipiainen-Seppänen O, Aho K. 1996. Incidence of rare systemic rheumatic and connective tissue diseases in Finland. *J Intern Med.* 240(2), p. 81–4.

Kakkar V, Assassi S, Allanore Y, Kuwana M, Denton C, Khanna D et al. 2022. Type 1 interferon activation in systemic sclerosis: a biomarker, a target of culprit. *Curr Opin Rheumatol.* 34(6), p. 357–64.

Kang G, Jung K, Lee Y, Kim H, Yoon D, Lee S et al. 2018. Incidence, prevalence, mortality and causes of death in systemic sclerosis in Korea: a nationwide population-based study. *Br J Dermatol*. 178(1), p. e37–39.

Kauppi M, Karjalainen A, Pirilä L, Puolakka K, Sokka-Isler T, Vähäsalo P. 2023. Reumasairaudet. *Duodecim*

Kawaguchi Y, Kuwana M. 2023. Pathogenesis of vasculopathy in systemic sclerosis and its contribution to fibrosis. *Curr Opin Rheumatol.* 35(6), p. 309–16.

Kelsey C, Torok K. 2013. The localized scleroderma assessment tool (LoSCAT): Responsiveness to change in a pediatric clinical population. *J Am Acad Dermatol.* 69(2), p. 214–20.

Khan K, Xu S, Nihtyanova S, Derrett-Smith E, Abraham D, Denton C, Ong V. 2012. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. *Ann Rheum Dis.* 71(7), 1235–42.

Khanna D, Denton C, Jahreis A, van Laar J, Frech T, Anderson M et al. 2016. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomized, controlled trial. *Lancet.* 387, p. 2630–40.

Khanna D, Furst D, Clements P, Allanore Y, Baron M, Czirjak L et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord.* 2(1), p. 11–8.

Khanna D, Lin C, Furst D, Goldin J, Kim G, Kuwana M et al. 2020. Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 8(10), p. 963–74.

Khanna D, Tashkin D, Denton C, Renzoni E, Desai S, Varga J 2020. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J of Res and Crit Care Med.* 201(6), p. 650–60.

Khatri S, Torok K, Mirizio E, Liu C, Astakhova K. 2019. Autoantibodies in Morphea: an update. *Front Immunol*. 10:1487.

Knobler R, Geroldinger-Simic M, Kreuter A, Hunzelmann N, Moinzadeh P, Rongioletti F et al.2024. Consensus statement on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: Localized scleroderma, systemic sclerosis and overlap syndromes. *J Eur Acad Dermatol Venereol.*00, p. 1–30.

Kroft E, Groeneveld T, Seyger M, de Jong E. 2009. Efficacy of topical tacrolimus 0.1% in active plaque morphea. *Am J Clin Dermatol.* 10(3), p. 181–7.

Kucharz E, Kopec-Medrek M. 2017 Systemic sclerosis sine scleroderma. *Adv Clin Exp Med.* 26(5), p. 875–80.

Kuo C-F, See L-C, Yu K-H, Chou I-J, Tseng W-Y, Chang H-C. 2011. Epidemiology and mortality of systemic sclerosis: a nationwide population study in Taiwan. *Scand J Rheumatol.* 40(5), p. 373–8.

Kumar A, Blixt E, Drage L, el-Azhary R, Wetter D. 2019. Treatment of morphea with hydroxychloroquine: a retrospective review of 84 patients at Mayo Clinic, 1996-2013. *J Am Acad Dermatol*. 80(6), p. 1658–63.

Kurzinski K, Zigler C, Torok K. 2019. Prediction of disease relapse in a cohort of paediatric patients with localized scleroderma. *Br J Dermatol.* 180(5), p. 1183–9.

Kuwana M. 2017. Circulating anti-nuclear antibodies in systemic sclerosis: Utility in diagnosis and disease subsetting. *J Nippon Med Sch.* 84(2), p. 56–63.

Kähäri V-M, Sandberg M, Kalimo H, Vuorio T, Vuorio E. 1988.Identification of fibroblasts responsible for increased collagen production in localized scleroderma by in-situ hybridization. *J Invest Dermatol.* 90(5), p. 664–70.

Le E, Wigley F, Shah A, Boin F, Hummers L. 2011. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. *Ann Rheum Dis.* 70(6), p. 1104–7.

Leitenberger J, Cayce R, Haley R, Adams-Huet B, Bergstresser P, Jacobe H. 2009. Morphea subtypes are distinct autoimmune syndromes: A review of 245 adult and pediatric cases. *Arch Dermatol* 145(5), p. 545–50.

Lepri G, Airò P, Disler O, Andreásson K, Braun-Moscovici Y, Hachulla E et al. 2023. Systemic sclerosis and primary biliary cholangitis: Longitudinal data to determine the outcomes. *JSRD*. 8(3), p. 210–20.

Lepri G, Bellando Randone S, Matucci Cerinic M, Allanore Y. 2019. Systemic sclerosis and primary biliary cholangitis: An overlapping entity? *JSRD.* 4(2), 111–7.PA

LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. 1988. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol.* 15(2), p. 202–5.

LeRoy E, Medsger T. 2001. Criteria for the classification of early systemic sclerosis. *J Rheumatol.* 28(7), p. 1573–6.

Lescoat A, Huang S, Carreira P, Siegert E, de Vries-Bouwstra J, Distler J et al. 2023. Cutaneous manifestations, clinical characteristics, and prognosis of patients with systemic sclerosis sine scleroderma data from the international EUSTAR database. *JAMA Dermatol*. 159(8), 837–47.

Liakouli V, Verde I, Ruscitti P, Di Vico C, Ruggiero A, Mauro D. 2024. Clinical and subclinical atherosclerosis in patients with systemic sclerosis: an observational, multicentre study of GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale). *Clin Exp Rheumatol.* 42, p. 1645–55.

LoMonaco A, Bruschi M, La Corte R, Volpinari, S,Trotta F. 2011.Epidemiology of systemic sclerosis in a district of northern Italy. *Clin Exp Rheumatol.* 29(2 Suppl 65), p. S10–S14.

López-Isac E, Acosta-Herrera M, Kerick M, Assassi S, Satpathy A, Granja J et al. 2019. GWAS for systemic sclerosis identifies multiple risk loci and highlights fibrotic and vasculopathy pathways. *Nat Commun.* 10(1): 4955

Mahajan A, Vasquez-Machado M, Zangenah N, Sparks J, LaChance A. 2025. Distinct cancer riskprofiles in patients with systemic sclerosis with autoantibody stratification. *Arthritis Rheumatol* .0(0), pp. 1–8

Maher T, Assassi S, Azuma A, Cottin V, Hoffmann-Vold A-M, Kreuter M et al. 2025. Nerandomilast in patients with progressive pulmonary fibrosis. *N Engl J Med.* 392(22), p. 2203–14.

Maher T, Tudor V, Saunders P, Gibbons M, Fletcher S, Denton C et al. 2023.Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease- associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomized, controlled, phase 2b trial. *Lancet Respir Med.* 11(1), p. 45–54.

Man A, Zhu Y, Zhang Y, Dubreuil M, Rho Y, Peloquin C et al. 2013. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. *Ann Rheum Dis.* 72(7), p. 1188–93.

Mankikian J, Caille A, Reynaud-Gaubert M, Agier M, Bermudez J, Bonniaud P et al. 2023. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. *Eur Resp J* . 61(6): 2202071

Marie I, Ducrotte P, Denis P, Menard J-F, Levesque H. 2009. Small intestinal bacterial overgrowth in systemic sclerosis. *Rheumatology.* 48(10), p. 1314–19.

Martel M-E, Leurs A, Launay D, Behal H, Chepy A, Collet A et al. 2024. Prevalence of anti-Ro52-kDa/SSA (TRIM21) antibodies and associated clinical phenotype in systemic sclerosis: Data from a French cohort, a systematic review and meta-analysis. *Autoimmun Rev.* 23(2024)103536.

Martini G, Saggioro L, Culpo R, Vittadello F, Meneghel A, Zulian F. 2021. Mycophenolate mofetil for methotrexate-resistant juvenile localized scleroderma. *Rheumatology.* 60(3), p. 1387–91.

Masi AT, Rodnan GP, Medsger TA Jr. 1980. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum*. 23(5), p. 581–90.

Matsuda K, Yoshizaki A, Kuzumi A, Toyama S, Awaji K, Miyake T et al. 2023. Rapid improvement of systemic sclerosis-associated intestinal pseudo-obstruction with intravenousimmunoglobulin administration. *Rheumatology.* 62(9), p. 3139–45

Matucci-Cerinic M, Denton C, Furst D, Mayes M, Hsu V, Carpentier P et al. 2011. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* 70(1), p. 32–8.

Matucci-Cerinic M, Kahaleh B, Wigley F. 2013. Evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum.* 65(8) p. 1953–62.

Mayes M, Lacey J, Beebe-Dimmer J, Gillespie B, Cooper B, Laing T et al. 2003. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum.* 48(8), p. 2246–55.

McMahan Z, Kulkarni S, Chen J, Chen J, Xavier R, Pasricha P et al. 2023. Systemic sclerosis gastrointestinal dysmotility: risk factors, pathophysiology, diagnosis and management. *Nat Rev Rheumatol*. 19(3), p. 166–81.

Meier F, Frommer K, Dinser R, Walker U, Czirjak L, Denton C et al. 2012. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis*. 71, p. 1355–60.

Meiszterics Z, Timar O, Gaszner B, Faludi R, Kehl D, Czirják L et al. 2016. Early morphologic and functional changes of atherosclerosis in systemic sclerosis—a systematic review and meta-analysis. *Rheumatology*. 55(12), p. 2119–30.

Mertens J, Seyger M, Kievit W, Hoppenreijs E, Jansen T, van den Kerkhof P et al. 2015. Disease recurrence in localized scleroderma: a retrospective analysis of 344 patients with paediatric- or adult-onset disease. *Br J Dermatol.* 172(3), p. 722–8.

Mihai C, Landewé R, van der Heijde D, Walker U, Constantin P, Gherghe A et al. 2015. Digital ulcers predict a worse disease course in patients with systemic sclerosis. *Ann Rheum Dis*. 75, 681–6.

Moelleken M, Kiesler B, Hadaschik E, Dissemond J. 2023. Successful therapy of ulcerative morphea with topical application of pimecrolimus. *J Eur Acad Dermatol Venereol.* 37, e325–6.

Moinzadeh P, Fonseca C, Hellmich M, Shah A, Chighizola C, Denton C et al. 2014. Association of anti-RNA polymerase III autoantibodies and cancer in scleroderma. *Arthritis Res Ther*. 16:R53.

Moinzadeh P, Kuhr K, Siegert E, Blank N, Sunderkoetter C, Henes J et al. 2020. Scleroderma renal crisis: Risk factors for an increasingly rare organ complication. *J Rheumatol*. 47(2), p. 241–8.

Morrisroe K, Hansen D, Huq M, Stevens W, Sahhar J, Ngian G et al. 2020. Incidence, risk factors, and outcomes of cancer in systemic sclerosis. *Arthritis Care Res.* 72(11), p. 1625–35.

Morrisroe K, Stewens W, Sahhar J, Rabusa C, Nikpour M, Proudman S et al. 2017. Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme. *Arthritis Res Ther.* 19(1), 19:42.

Mouthon L, Bussone G, Berezné A, Noël LH, Guillevin L. 2014. Scleroderma renal crisis. *J Rheumatol*. 41(6), p. 1040–8.

Mukerjee D, St George D, Coleiro B, Knight C, Denton C, Davar J et al. 2003. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis*. 62, p. 1088–93.

Murray K, Laxer R. 2002. Scleroderma in children and adolescents. *Rheum Dis Clin North Am*. 28(3), p. 603–24.

Mähönen K, Keskitalo S, Salokas K, Tuhkala A, Panelius J, Ranki A et al. 2024. Mass-spectrometry-based proteomic analysis of the skin of patients with localized scleroderma. *J Dermatol Sci.* 113(3), p. 148–50.

Mähönen K, Mogollon I, Hassinen A, Polso M, Välimäki K, Potdar S et al. 2025. High-content image-based drug testing of patients' primary fibroblasts reveals potential new treatment options for localized scleroderma. *Acta Derm Venereol.* 105:43088.

Nassar M, Ghemautan V, Nso N, Nyabera A, Castillo F, Tu W. 2022. Gastrointestinal involvement in systemic sclerosis: An updated review. *Medicine.* 101(45), e31780.

Nihtyanova S, Sari A, Harvey J, Leslie A, Derrett-Smith E, Fonseca C, et al. 2020. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. *Arthritis Rheumatol.* 72(3), p. 465–76.

Nihtyanova S, Tang E, Coghlan J, Wells A, Black C, Denton C. 2010. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study.*Q J Med.* 103(2), p. 109–15.

Nunes J, Cunha A, Meirinhos T, Nunes A, Araújo P, Godinho A. 2018. Prevalence of auto-antibodies associated to pulmonary arterial hypertension in scleroderma – A review. *Autoimmun Rev.* 17(12), p. 1186–201.

Pakozdi A, Nihtyanova S, Moinzadeh P, Ong V, Black C, Denton C. 2011. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. *J Rheumatol.* 38(11), p. 2406–9.

Paltta J, Kortelainen S, Käyrä M, Piriä L, Huhtakangas J, Palomäki A. 2023. The validity of systemic sclerosis diagnoses in two university hospitals in Finland. *Scand J Rheumatol.* 52(1), 84–7.

Papara C, De Luca D, Bieber K, Vorobyev A, Ludwig R. 2023. Morphea: The 2023 update. *Front Med.* 10: 1108623.

Parodi A, Sessarego M, Greco A, Bazzica M, Filaci G, Setti M et al. 2008. Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. *Am J Gastroenterol.* 103(5), p. 1257–62.

Patel S, Morrisroe K, Proudman S, Hansen D, Sahhar J, Sim M et al. 2020. Occupational silica exposure in an Australian systemic sclerosis cohort. *Rheumatology.* 59(12), p. 3900–5.

Pauling J, McHugh N, McGrogan A. 2025. Systemic sclerosis and cancer in the UK: an epidemiological analysis using the clinical practice research datalink. *Rheumatology*. 64(4), p. 1959–65.

Peng H, Wu X, Wen Y, Li C, Lin J, Li J et al. 2020. Association between systemic sclerosis and risk of lung cancer: results from a pool of cohort studies and Mendelian randomization analysis. *Autoimmun Rev.* 19. 102633.

Perelas A, Silver R, Arrossi A, Highland K. 2020. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med.* 8(3), p. 304–20.

Peterson L, Nelson A, Su W, Mason T, O'Fallon W, Gabriel S. 1997. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993. *J Rheumatol*. 24(1), p. 73–80.

Pope J, Bellamy N, Seibold J, Baron M, Ellman M, Carette S et al. 2001. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum.* 44(6), p. 1351–8.

Pope J, Denton C, Johnson S, Fernandez-Codina A, Hudson M, Nevskaya T. 2023. State-of-the-art evidence in the treatment of systemic sclerosis. *Nat Rev Rheumatol*. 19(4), p. 212–26.

Richard N, Gyger G, Hoa S, Proudman S, Stevens W, Nikpour M. 2021. Immunosuppression does not prevent severe gastrointestinal tract involvement in systemic sclerosis. *Clin Exp Rheumatol.* 39(4), p. S142–S148.

Richard N, Hudson M, Wang M, Gyger G, Proudman S, Stevens W et al. 2019. Severe gastrointestinal disease in very early systemic sclerosis is associated with early mortality. *Rheumatology*. 58(4), p. 636–44.

Rigamonti C, Shand L, Feudjo M, Bunn C, Black C, Denton C et al. 2006. Clinical features and prognosis of primary biliary cirrhosis associated with systemic sclerosis. *Gut.* 55(3), p. 388–94.

Roofeh D, Lin C, Goldin J, Kim G, Furst D, Denton C et al. 2021. Tocilizumab prevents progression of early systemic sclerosis associated interstitial lung disease. *Arthritis Rheumatol.* 73(7), p. 1301–10.

Rosenberg A, Uziel Y, Krafchik B, Hauta S, Prokopchuk P, Silverman E et al. 1995. Antinuclear antibodies in children with localized scleroderma. *J Rheumatol.* 22(12), p. 2337–43.

Roustit M, Blaise S, Allanore Y, Carpentier P, Caglayan E, Cracowski JL. 2013. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis* 72(10), p. 1696–9.

Rubio-Rivas M, Royo C, Simeon C, Corbella X, Fonollosa V. 2014. Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. *Semin Arthritis Rheum*. 44(2), p. 208–19.

Rutka K, Garkowski A, Karaszewska K, Lebkowska U. 2021.Imaging in diagnosis of systemic sclerosis. *J Clin Med.* 10(2), p. 1–15.

Salazar G, Assassi S, Wigley F, Hummers L, Varga J, Hinchcliff M, et al. 2015. Antinuclear antibody-negative systemic sclerosis. *Seminars in arthritis and rheumatism*. 44(6), p. 680–6.

Santos C, Del Galdo F. 2025. New horizons in systemic sclerosis treatment: advances and emerging therapies in 2025. *RMD Open*. 11(3) e005776.

Sari A, Satis H, Ayan G, Küçüksahin O, Kalyoncu U, Fidanci A et al. 2024. Survival in systemic sclerosis associated pulmonary arterial hypertension in the current treatment era-results from a nationwide study. *Clin Rheumatol.* 43(6), p. 1919–25.

Scherlinger M, Lutz J, Galli G, Richez C, Gottenberg J-E, Sibilia J et al. 2021. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments. *Semin Arthritis Rheum*. 51(1), p. 36–42.

Seghal V, Srivastava G, Aggarwal A, Behl B, Choudhary M, Bajaj P. 2002. Localized scleroderma/morphea.*Int J Dermatol.* 41, p. 467–475.

Sener S, Batu E. 2025. Use of biologic drug in the treatment of localized scleroderma and systemic sclerosis in children: A scoping review. *Semin Arthritis Rheum*. 71, 152634.

Seyger M, van den Hoogen F, de Boo T, de Jong E. 1998. Low-dose methotrexate in the treatment of widespread morphea. *J Am Acad Dermatol.* 39(2 Pt 1), p. 220–5.

Silman A, Jannini S, Symmons D, Bacon P. 1988. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol.*27(4), p. 286–90.

Simeon-Aznar C, Tolosa-Vilella C, Gabarro-Julia L, Campillo-Grau M, Guillen Del Castillo A, Fonollosa-Pla V et al. 2014. Systemic sclerosis sinen scleroderma and limited cutaneous systemic sclerosis: similarities and differences. *Clin Exp Rheumatol*. 32(6), p.33–40

Smith V, Herrick A, Ingegnoli F, Damjanov N, De Angelis R, Denton C et al. 2020. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud′s phenomenon and systemic sclerosis. *Autoimmun Rev*. 19(3)

Smith V, Ickinger C, Hysa E, Snow M, Frech T, Sulli A et al. 2023. Nailfold capillaroscopy. *Best Pract Res Clin Rheumatol.* 37(1)

Smith V, Riccieri V, Pizzorni C, Decuman S, Deschepper E, Bonroy C et al. 2013. Nailfold capillaroscopy for prediction of novel future severe organ involvement in systemic sclerosis. *J Rheumatol* 40(12), p. 2023–8.

Smith V, Vanhaecke A, Herrick A, Distler O, Guerra M, Denton C et al. 2019. Fast track algorithm: How to differentiate a "scleroderma pattern" from a "non-scleroderma pattern". *Autoimmun Rev*.18(11) 102394.

Steen V. 2005. Autoantibodies in Systemic Sclerosis. *Semin Arthritis Rheum*. 35(1), p. 35–42.

Steen V. 2003. Scleroderma renal crisis. *Rheum Dis Clin N Am* 29, p. 315–33.

Steen V, Medsger T. 2007. Changes in causes of death in systemic sclerosis. *Ann Rheum Dis.* 66(7), p. 940–4.

Steen V, Medsger T Jr. 2003. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum*. 48(2), p. 516–22.

Steen V, Medsger T Jr. 2000. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.* 43(11), p. 2437–44.

Steen VD, Oddis C V, Conte CG, Janoski J, Casterline GZ, Medsger TA. 1997. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963-1982. *Arthritis Rheum*. 40(3), p. 441–5.

Steen V, Powell D, Medsger T Jr, 1988. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum*. 31(2), p. 196–203

Stochmal A, Czuwara J, Trojanowska M, Rudnicka L,2020. Antinuclear antibodies in systemic sclerosis: an update. *Clinic Rev Allerg Immunol*. 58, p. 40–51.

Sulli A, Paolino S, Pizzorni C, Ferrari G, Pacini G, Pesce G et. al. 2020. Progression of nailfold capillaroscopic patterns and correlations with organ involvement in systemic sclerosis: a 12 year study. *Rheumatology.* 59(5), p. 1051–8.

Sulli A, Pizzorni C, Smith V, Zampogna G, Ravera F, Cutolo M. 2012. Timing of transition between capillaroscopic patterns in systemis sclerosis. *Arthritis Rheum*. 64(3), p. 821–5.

Sulli A, Secchi M E, Pizzorni C, Cutolo M. 2008. Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. *Ann Rheum Dis.* 67(6), p. 885–7.

Tandaipan J, Guillén-Del-Castillo A, Simeón-Aznar C, Carreira P, De la Puente C, Narváez J et al. 2023. Immunoglobulins in systemic sclerosis management. A large multicenter experience. *Autoimmun Rev*. 22, 103441.

Tashkin D, Elashoff R, Clements P, Goldin J, Roth M, Furst D et al. 2006. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 354(25), p. 2655–66.

Tashkin D, Roth M, Clements P, Furst D, Khanna D, Kleerup E et al. 2016. Mycophenolate mofetil versus oral cyclophoshamide in scleroderma-related interstitial lung disease: scleroderma lung study II (SLS-II), a double-blind, parallel group, randomised controlled trial. *Lancet Respir Med.*4(9), p. 708–19.

Teske N, Fett N. 2024. Recent advances in treatment of systemic sclerosis and morphea. *Am J Clin Dermatol.* 25(2), p. 213–26.

Tian X, An P, Liu R, Zuo W, Liu X, Song Z. 2025. Efficacy of cyclophosphamide for skin fibrosis in systemic sclerosis: a systematic review and single-arm meta-analysis. *Eur J Clin Pharmacol*. doi: 10.1007/s00228–025-03837–3.

Tingey T, Shu J, Smuczek J, Pope J. 2013. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. *Arthritis Care Res*. 65(9), p. 1460–71.

Tolosa-Vilella C, Del mar rodero-Roldan M, Guillen-Del-Castillo A, Marin-Ballve A, Boldova-Aguar R, Mari-Alfonso B et al. 2023.Nailfold videocapillaroscopy patterns in systemic sclerosis: implications for cutaneous subsets, disease features and prognostic value for survival. *Clin Exp Rheumatol*. 41(8), p. 1695–703.

Tyndall A, Bannert B, Vonk M, Airò P, Cozzi F, Carreira P. 2010. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 69(10), p.1809–15.

Tyndall A, Fistarol S, 2013. The differential diagnosis of systemic sclerosis. *Curr Opin Rheumatol*. 25(6), p. 692–9.

Uitto J, Bauer E, Eisen A. 1979. Scleroderma: increased synthesis of of triple-helical type I and type III procollagens associated with unaltered expression of collagenase by skin fibroblasts in culture.*J Clin Invest*. 64(4), p. 921–30.

Uitto J, Øhlenslager K, Lorenzen I. 1971. Solubility of skin collagen in normal human subjects and in patients with generalized scleroderma. *Clin Chim Acta.*31(1), p. 13–8.

Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Arthritis Rheum.* 65(11), p. 2737–47.

Van Laar J, Farge D, Sont J, Naraghi K, Marjanovic Z, Larghero J et al. 2014. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. A randomized clinical trial. *JAMA.* 311(24), p. 2490–98.

Van Leeuwen N, Boonstra M, Fretheim H, Brunborg C, Midtvedt O, Garen T et al. 2022.Gastrointestinal symptom severity and progression in systemic sclerosis. *Rheumatology*. 61(10), p. 4024–34.

Vanhaecke A, Cutolo M, Distler O, Riccieri V, Allanore Y, Denton C et al. 2022. Nailfold capillaroscopy in SSc: innocent bystander or promising biomarker for novel severe organ involvement/progression? *Rheumatology.* 61(11), p. 4384–96.

Vanhaecke A, De Schepper S, Paolino S, Heeman L, Callens H, Gutermuth J. 2020. Coexistence of systemic and localized scleroderma:a systematic literature review and observational cohort study. *Rheumatology.* 59(10), p. 2725–33.

Velauthapillai A, Bootsma M, Bruni C, Bergmann C, Matucci-Cerinic M, Launay D et al. 2024. Preventive effects of early immunosuppressive treatment on the development of interstitial lung disease in systemic sclerosis. *Rheumatology*. 00, p. 1–9.

Vignaux O, Allanore Y, Meune C, Pascal O, Dupoc D, Weber S et al. 2005. Evaluation of the effect of nifedipine upon myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue Doppler echocardiography in systemic sclerosis. *Ann Rheum Dis.* 64(9), p. 1268–73.

Vigone B, Caronni M, Severino A, Bellochi C, Baldassarri A, Fraquelli M et al. 2017. Preliminary safety and efficacy profile of prucalopride in the treatment of systemic sclerosis (SSc)-related intestinal involvement: results from the open label cross-over PROGASS study. *Arthritis Res Ther*. 19(1), 145

Volkmann E, McMahan Z. 2022. Gastrointestinal involvement in systemic sclerosis: pathogenesis, assessment and treatment. *Curr Opin Rheumatol*. 34(6), p. 328–36.

Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk APJ, et al. 2009. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. *Ann Rheum Dis.* 68(6), p. 961–5.

Vonk M, Marjanovic Z, van den Hoogen F, Zohar S, Schattenberg A, Fibbe W. 2008. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. *Ann Rheum Dis.* 67(1), p. 98–104.

Watanabe T, Ototake Y, Akita A, Suzuki M, Kanaoka M, Tamura Y, et al. 2024. Clinical features of patients with systemic sclerosis positive for anti-SS-A antibody: a cohort study of 156 patients. *Arthritis Res Ther.* 26:93

Wirz E, Jaeger V, Allanore Y, Riemekasten G, Hachulla E, Distler O. 2016. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. *Ann Rheum Dis.* 75(7), p. 1285–92.

Wu J, Zhang X, Lin S, Wei Q, Lin Z, Jin O et al. 2024. Alterations in peripheral T- and B-cell subsets in patients with systemic sclerosis. *Int J Rheum Dis.* 27: e15145.

Yan Q, Bruni C, Garaiman A, Mihai C, Jordan S, Becker M et al. Post hoc comparison of tocilizumab, rituximab, mycophenolate mofetil, and cyclophosphamide in patients with SSc-ILD from the EUSTAR database. *Ann Rheum Dis*. 84, p. 620–31.

Yan W, Cai J, Lu F. 2025. Plastic surgery interventions for localized scleroderma deformities: an evidence synthesis. *Aesth Plast Surg*. doi: 10.1007/s00266–025–05138–7

Zamanian R, Badesch D, Chung L, Domsic R, Medsger T, Pinckney A et al. 2021. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis–associated pulmonary arterial hypertension. A multicenter, double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 204(2), p. 209–21.

Zhong L, Pope M, Shen Y, Hernandez J, Wu L. 2019. Prevalence and incidence of systemic sclerosis: A systematic review and meta-analysis. *Int J Rheum Dis*. 22(12), p. 2096–107.

Zulian F, Athreya B, Laxer R, Nelson A, Feitosa de Oliveira S, Punaro M. 2006. Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology.* 45(5), p. 614–20.

Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A et al. 2011. Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 63(7), p. 1998–2006.

Zulian F, Vallongo C, Woo P, Russo R, Ruperto N, Harper J et al. 2005. Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum.* 52(9), p. 2873–81.

List of Figures and Tables

Figures

Tables

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2026

ISBN 978-952-02-0624-6 (PRINT)
ISBN 978-952-02-0625-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)