Review

Systemic sclerosis: one year in review 2022

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ABSTRACT

Systemic sclerosis (SSc) is an autoimmune disease characterised by microvasculopathy, immune dysregulation, and skin and visceral organ fibrosis. Every year novel insights into the pathogenesis, organ involvement and treatment of this severe disease are published in the scientific community. In this review we report an overview of some of the most relevant contributions published in 2021.

Introduction

Systemic sclerosis (SSc) is a rare, complex, and chronic disease. Diagnosing the disease at an early stage is crucial for the treatment of diffuse cutaneous involvement and of other troublesome complications, such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) (1). Following the previous editorial initiatives of Clinical and Experimental Rheumatology to present novel relevant insights on rheumatic diseases in the form of "One year in review" (2, 3), we provide a review of the most significant contributions published in 2021 regarding SSc affecting adult patients. A MedLine search was performed using the term "systemic sclerosis" (MeSH terms and semantic search), focusing on pathogenesis, clinical manifestations, and treatment. We included 109 articles in English published between January 1st, 2021 and December 31th, 2021.

Pathogenesis of SSc

Genetics

Clark *et al*. analysed the transcriptome of skin biopsies of patients with early diffuse cutaneous SSc (dcSSc) and found 61 genes whose expression differed between patients with anti-RNA polymerase III antibodies (ARA) and those with anti-topoisomerase I antibodies (ATA). Those with ARA seemed to be more influenced by impairment of local connective tissue and adipocytes, whereas those with ATA seemed to reflect more persistent or refractory immune cell-driven skin fibrosis (4). A comparison of mRNA extracted from SSc myofibroblasts and non-myofibroblastic cells revealed a higher expression of NBPF genes in the former, suggesting a role of the NBPF cluster in SSc pathogenesis (5). A Japanese study found that CD16+ monocytes differed between SSc and healthy controls, and that they expressed a group of inflammatory genes that is thought to be relevant in SSc pathogenesis (6). A Spanish study analysed 59 SSc patients with PAH and identified pathogenic or likely pathogenic mutations in potassium channel genes (KCNK5 and ABCC8) (7). It was demonstrated that homozygosity for rs2235611, a SNP of SRp55, which is the regulatory splicing factor responsible for the switch from proangiogenic VEGF-A165 to antiangiogenic VEGF-A165b, significantly influences the predisposition to develop SSc. Furthermore, it was strictly associated with ILD and with a nailfold videocapillaroscopy (NVC) "late" pattern (8). Another study investigated the expression of quantitative trait loci (eQTL) potentially specific to SSc and found that some transcription factors are differentially expressed in disease-relevant tissues: ELF1 and MGA were upregulated in SSc blood cells, KLF4 and ID4 were downregulated in SSc skin, and TBX4 was upregulated in SSc lungs (9). A multi-centric study generated a GRS (genomic risk score) based on the allelic effects identified in the largest SSc genome-wide association study to date; this proved able to discriminate between SSc and healthy controls with a remarkable predictive value, and between SSc and other immune-mediated inflammatory diseases (10).

Regarding epigenetics, Zehender *et al*. demonstrated that TGF-β determined a SMAD3-dependent downregulation of MYST1, a histone acetyltransferase that normally downregulates the expression of core components of the autophagy machinery in fibroblasts, ultimately leading to an aberrant activation of autophagy in SSc and promoting collagen release (11).

Cells and cytokines

Several studies have focused on the dysregulation of the innate immune system occurring in SSc. Andreucci *et al*. demonstrated that SSc dermal fibroblasts (DFs) were largely dependent on glycolysis, with consequent large production of lactates and acidification of the microenvironment. In this acidic microenvironment, endothelial cells upregulated matrix metalloproteinase-12 (MMP-12) and caused an increased degradation of urokinase-type plasminogen activator receptor (uPAR), leading to an impaired angiogenesis in SSc. Furthermore, acidic pH promoted the differentiation of endothelial cells into myofibroblasts, in a process called endoMT (12). Rudnik *et al*. co-cultured CD14+ monocytes with DFs from SSc patients and from healthy controls (HCs) and observed a significantly increased expression of profibrotic genes (ACTA2, COL1A1, alfaSMA and FN1) in the monocytes of the SSc culture (13). Another study analysed the mechanism of adhesion and infiltration of CD14+ monocytes. SSc monocytes had a higher expression of adhesion molecules (CCL2 and CCL3, CXCR1 and CXCR2, SELPLG, and ITGB2) and downregulated expression of CD52. The study demonstrated that CD52 blockade with the anti-CD52 antibody Alemtuzumab resulted in increased adhesion. Interestingly, the exposure to type I and type II Interferon (INFs), regulated by the histone deacetylase (HDAC) family, diminished the expression of CD52. A selective inhibition of HDAC IIa resulted in an upregulation of CD52, identifying an IFN–HDAC–CD52 axis that could be targeted by specific therapy (14).

A Japanese group investigated the role of interleukin-31 (IL-31), which had previously been implicated in fibrosis and in T-helper (Th) 2-mediated immunity. Serum IL-31 levels were significantly elevated in SSc patients compared with HCs and were positively correlated with modified Rodnan skin score (mRSS), and negatively correlated with % diffusing capacity for carbon monoxide (DLco). Samples of skin damaged by SSc showed significantly higher mRNA levels of IL-31 and IL-31RA compared with the skin of HCs (15). A French study found that the absolute number of circulating type 2 innate lymphoid cells (ILC2) were approximately three times lower in SSc compared with HCs, whereas a significant increase in ILC2 was observed in SSc patients, with a positive correlation with skin fibrosis. SSc skin samples showed a low percentage of KLRG1, a marker associated with the inflammatory form of ILC2. In a mouse model of SSc, therapeutic intervention combining pirfenidone with IL-10 reduced the numbers of skin-infiltrating ILC2, enhancing their expression of KLRG1 and strongly alleviating skin fibrosis (16).

Take home messages

- Several mechanisms involved in SSc pathogenesis have been investigated, such as the high expression of NPBF cluster genes in myofibroblasts (5), potassium channel dysfunction (7), TGF-β-induced enhancement of autophagy (11), and pathways involving immune-mediated fibrosis (13, 16).
- The acidic microenvironment in SSc may lead to transition of monocytes into myofibroblast-like cells, to the impairment of neoangiogenesis, and to the transition of endothelial cells into myofibroblasts (12).
- Dysregulated innate immune response in SSc may represent a potential target for novel therapies, such as alemtuzumab (14).

Clinical manifestations and organ involvement

Early diagnosis is important to avoid irreversible damage, and the identification of more homogeneous subsets of SSc patients is a crucial target in SSc research (17). Results from the multicentric SSc cohort of 2281 patients - including 247 men - recruited in the Italian Systemic Sclerosis PRogression INvestiGation (SPRING) registry were published. The study showed significant sex-related differences in several aspects of SSc, including more severe disease in men, who presented with extensive skin involvement, digital vasculopathy, and internal organ involvement, and a higher prevalence of sicca syndrome and an autoantibody profile characterised by serum ANA, anti-ENA, anti-CENP-B, and anti-La/SSB antibodies in female patients (18). The analysis of the largest cohort of anti-PM/Scl+ patients from the European Scleroderma Trials and Research Group (EUSTAR) database identified a specific clinical subset of SSc patients characterised by muscle involvement, dermatomyositis, calcinosis and ILD with a good prognosis (19). Long-term data from a recent retrospective study on 375 SSc patients confirmed male sex, DLco <70%, cardiac involvement, and C-reactive protein (CRP) >5mg/l as independent predictors of mortality. *Sine scleroderma* subtype had better survival than diffuse or limited cutaneous subtypes (20).

Lescoat *et al*. summarised symptoms and domains mentioned by lcSSc patients to design a future combined response index dedicated to lcSSc. The most salient reported domains were skin, musculoskeletal, cardiac, pulmonary, GI manifestations, sleep, fatigue, Raynaud's phenomenon (RP), and digital ulcers (DUs) (21).

Pain is one of the most common chief complaints in patients with SSc and correlates with age, gender, DUs, small-joint contractures, and GI symptoms (22). Disease-specific determinants that influence health-related quality of life have been described in 492 SSc patients. PAH, DUs, RP and GI involvement significantly contributed to the worsening of quality of life over time (23).

Patients with SSc may require considerable healthcare resources with a notable economic impact over time (24). A recent systematic review showed that the management of the dcSSc subtype had higher costs than lcSSc (25).

Vascular manifestations

Vascular complications are still responsible for significant mortality and

morbidity in patients with SSc (26). Recently, bilateral Doppler ultrasonography of carotid, vertebral, and peripheral arteries was performed on 88 SSc patients; atheromatous plaques were found in 67.7% of 1936 arteries examined by Doppler ultrasonography. Of these, 37.4% demonstrated a narrowing of the intraluminal diameter, whereas the carotid intima-media thickness was increased in 55.7% of the patients. This degree of thickness correlated with disease duration, mRSS, and the Medsger Disease Activity Score, but not with cardiovascular risk factors (27).

Early detection at a subclinical stage with carotid femoral pulse wave velocity may be helpful in SSc therapeutic planning and management (28).

NVC is a well-established tool that can quantify structural vascular abnormalities in SSc. Digital thermal monitoring was tested in 31 SSc patients for the assessment of microvascular dysfunction related to thermoregulation. Vascular reactivity index was progressively higher in SSc patients with early, active, and late NVC patterns of microangiopathy, with a significant negative correlation between vascular reactivity index and microhaemorrhage scores. NVC and digital thermal monitoring may quantify different aspects of vasculopathy and may enrich each other as diagnostic tools (29). Furthermore, digital thermal monitoring may identify patients at risk for DUs, as recently confirmed in a study on 90 patients where the vascular reactivity index was lower in patients with DUs (30). Gigante *et al*. proposed laser speckle contrast analysis (LASCA) as a method for the evaluation of peripheral blood perfusion of the hands, suggesting that it could be used along with NVC to define different vascular phenotypes of SSc. In their retrospective study on 176 SSc patients, proximal-distal gradient predicted major vascular complications (DUs, PAH, SRC) and 5-year mortality of SSc patients (31). Another recent study found that arterial stiffening and cardiovascular risk scores were positively associated with the degree of progression of peripheral microvasculopathy assessed with NVC, suggesting an association between NVC abnormalities and higher cardiovascular risk in SSc patients (32). Cassius *et al*. assessed the frequency of lower limb arterial impairment in SSc patients by measuring ankle-brachial index, toe pressure, and toe-brachial index, showing that 76% of SSc patients had hemodynamic arterial lower limb abnormalities related to macro- and/or microvascular impairment, and that 28% had vascular stiffness (33).

Pulmonary arterial hypertension

PAH is currently the main cause of death in SSc. A systematic review and meta-analysis reported an overall PAH prevalence and incidence of 6.4% and 18.2 cases per 1000 person-years, respectively (34). The main tool to screen for PAH is transthoracic echocardiography with a sensitivity of 90%, even if definitive diagnosis should be confirmed by right heart catheterisation (RHC) (35).

The DETECT algorithm is an evidence-based screening algorithm created in 2013 which can be used as a screening tool for SSc-PAH because of its high sensitivity and negative predictive value in patients with a DLco ≥60% (36).

Showalter *et al*. evaluated the number of hospital readmissions among individuals with SSc and PH enrolled in the PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) registry, a large North American registry of SSc patients at risk for or with incident PAH, and reported that 34% of the individuals with SSc-PH (or with SSc at high-risk for PH) had ≥1 hospital readmission within 12 months (37).

Tona *et al*. reported that ventricular-arterial coupling by 3-dimensional echocardiography could be significantly higher in dcSSc patients than in lcSSc patients, despite normal LVEF (38). Although 2-dimensional echocardiography is a useful screening tool in PAH given its high specificity and high positive predictive value, right ventricular dysfunction and emerging PAH are often undetected or underestimated until late in the disease course. A novel non-invasive metric of regional and global right ventricular contractile function called right ventricular longitudinal systolic strain was recently shown to identify SSc patients with limitations in right ventricular reserve and poor clinical outcomes (39).

A morphological evaluation using echocardiography and cardiac MRI compared with hemodynamic evaluation by pulmonary arterial wedge pressure could better reflect the copresence of left heart disease phenotype in patients with SSc and PH (40). Dumitru *et al*. used cardiovascular MRI to characterise predictors of subclinical SSc-PAH in 83 SSc patients with no history of cardiovascular disease or PAH. Subclinical SSc-PAH was characterised by myocardial microvasculopathy, diffuse and focal myocardial fibrosis but preserved myocardial contractile function. This subclinical phenotype of SSc-PAH was associated with high-sensitivity troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), SSc disease severity and DUs (41).

Lui *et al*. proposed electrocardiography (ECG) as an inexpensive, widely available, non-invasive test for the evaluation of PAH in SSc patients, which could be potentially useful for risk stratification. They retrospectively evaluated the ECGs from 169 SSc patients: right axis deviation and left axis deviation was observed in 28.4% and 30.8% of patients with SSc-PH, respectively; both were associated with poor prognosis and with an increased hazard for mortality (42).

Cardiac involvement

Primary cardiac involvement in SSc includes conduction blocks, arrhythmias, and non-ischaemic cardiomyopathy. In a cohort of 806 SSc patients, disease duration, DLCO ≤60% and a history of SRC were associated with an increased risk of diastolic dysfunction (43). Heart failure with preserved ejection fraction (HFpEF) is a clinically relevant complication of SSc, and was reported in 25% of 155 SSc patients (44). Dumitru *et al*. evaluated cardiac MRI and NT-proBNP for the assessment of primary heart involvement in 74 SSc patients. The presence of cardiovascular disease was considerably higher in those with NT-proBNP >125 pg/mL, and a trend for poorer time-to-event was noted in

those with higher extracellular volume and hs-TnI levels (45). A prospective Chinese multi-centric cohort of 784 SSc patients showed a prevalence of left ventricular diastolic dysfunction of 31.4%, and identified advanced age of onset, PAH, anti-RNP antibodies, increased WBC count, and adverse metabolic status as risk factors for SSc-related left ventricular diastolic dysfunction (46).

Heart involvement in SSc may also be related to myocarditis. Serum anti-heart and anti-intercalated disk autoantibodies are organ- and disease-specific markers of isolated autoimmune myocarditis; they have recently been reported in asymptomatic SSc patients, suggesting underdiagnosed autoimmune heart involvement. In a recent study, they were associated with ILD, history of chest pain, abnormal troponin, and concurrent immunosuppression (47). The diagnostic work-up for myocardial impairment is usually conducted in the late stage. Novel sensitive methods are required for early diagnosis of myocardial impairment in SSc. In one study, global longitudinal strain measured by 2D speckle-tracking echocardiology (2D-STE) was proposed as a sensitive and practical method for early cardiac damage assessment, as approximately 25% out of 95 SSc patients presented a subclinical cardiac impairment that could be detected only by 2D-STE (48). Patients with SSc have a 4-fold increased prevalence of moderate/severe valvular heart disease at diagnosis and during follow-up compared to HCs. Aortic stenosis was the most prevalent valvulopathy along with secondary tricuspid regurgitation (49, 50).

Musculoskeletal manifestations

Two large French cohorts studied the prevalence of autoantibodies associated with erosive arthritis. Among 448 SSc patients, 25% had rheumatoid factor (RF), 9% had anti-citrullinated proteins antibodies (ACPA), and 14% had anti-carbamylated proteins (anti-CarP) antibodies. After a multivariate analysis, RF, ACPA, and anti-CarP antibodies resulted significantly associated to vascular complications, synovitis/tenosynovitis, and skin fibrosis, lung disease and DUs, respectively (51). Among 120 SSc patients enrolled in a recent cross-sectional study, acro-osteolysis was common in patients at early onset of the disease; it was positively associated with ATA, hand deformity and dysphagia, and negatively associated with skin oedema (52). In a cohort of patients with early disease (defined as <5 years of disease duration), acro-osteolysis and calcinosis were associated with lower patient-reported outcome measure (PROM) completion rates (53).

Cutaneous manifestations

The gold standard method for skin assessment in SSc is mRSS, which however is characterised by high interobserver variability. In a study on 53 patients, high-frequency ultrasound allowed objective assessment of cutaneous fibrosis in SSc with an excellent interobserver agreement and reproducibility for all parameters, along with the detection of subclinical abnormalities. These observations suggested the use of high-frequency ultrasound as an alternative to mRSS in clinical trials (54). In a study with 43 SSc patients, ultrasound was highly specific but less sensitive compared to radiographs for the detection of calcinosis cutis (55).

Neurological manifestations

Pure sensory polyneuropathy is the most prevalent type of neuropathy in SSc; other observed patterns are mixed sensory and motor polyneuropathy and mononeuritis multiplex. Recently, peripheral neuropathy was reported in 36.7% of 60 SSc patients. Of them, polyneuropathy and focal neuropathy were found in 23.3% and 13.3% of the patients, respectively (56). Recently, a case-control study reported an incidence rate of trigeminal neuralgia of 5.8 per 1000 person-years (57).

Renal manifestations

The risk of end-stage renal disease in a cohort of 2012 SSc patients was approximately two times higher than in the control group; male and younger patients were the most susceptible groups (58).

In one study from the EUSTAR database, it was reported that estimated glomerular filtration rate (eGFR) represented a predictive risk factor for overall survival in SSc but did not represent a risk factor for death from SRC (59). In a recent study, eGFR resulted to be a predictive marker of mortality for SSc, whereas RRI (renal resistive index) was a predictive marker of mortality for all causes (60). Cianci *et al*. reported higher RRI values in SSc patients (with renal scleroderma vasculopathy) with respect to IgA nephropathy patients (with glomerular injury), thereby reflecting that RRI expressed not only kidney damage but also microvascular alterations (61).

SRC is a severe manifestation of SSc, and is independently associated with African American ethnicity, which appears to also have a higher prevalence of anti-Ro antibodies (62).

Pulmonary involvement

ILD is a common manifestation of SSc and is associated with older age and male gender. HRCT and pulmonary function tests (PFTs) are crucial for diagnosis and for monitoring disease progression (63). Landini *et al*. performed a systematic review on chest CT findings as predictors of mortality or ILD progression in SSc-ILD. Extensive ILD may be a predictor of need for supplemental oxygen or of lung transplantation (64). Even if HRCT imaging, together with PFTs, is currently the gold standard for a cost-effective and non-invasive assessment of ILD, the inter-reader variability remains an issue. In contrast, radiomics is an objective imaging-based tool that enables a more detailed and reliable quantitative assessment of lesion features. Schniering *et al*. proposed a binary radiomic risk score composed of 26 features which accurately predicted progression-free survival (65). In a cohort of 60 patients, Martini *et al*. speculated that radiomics might capture features indicating severity of SSc-ILD on HRCT and claimed that radiomics could predict gender, age, and pulmonary function stage with a sensitivity of 84% and a specificity of almost 100% (66). Quantitative computed tomography (qCT) may become an objective tool for the assessment of ILD in SSc, complementary to PFTs

and visual fibrosis scores. The lung density and volume of 135 SSc patients were compared to HCs by a software-aided image segmentation method. It was demonstrated that lung density was higher in SSc patients with signs of ILD than those without ILD or HCs. It was also shown that, even in the absence of signs of pulmonary fibrosis on HRCT, lung density was higher in patients with dcSSc compared with both lcSSc patients and HCs (67). Furthermore, they reported that qCT parameters differentiated SSc patients with ILD showing a good correlation with visual fibrosis scores (68). Carnevale *et al*. showed that repeated HRCT after 12-24 months seemed useful for the longitudinal characterisation of ILD evolution in patients with stable pulmonary function. Moreover, they demonstrated that the OMERACT criteria might overlook patients with radiological progression (69). Roofeh *et al*. recently evaluated FVC and DLco using the OMERACT Filter 2.1, an evidence-based algorithm used to identify outcome measures that are truthful, feasible, and able to discriminate between groups of interest; they identified FVC to be endorsed for use in the setting of SSc-ILD clinical trials and longitudinal observational studies. DLco was not endorsed based on the working group's vote (70).

Lung ultrasound (LUS) and MRI were recently proposed for screening and follow-up in ILD-SSc patients (71). The UTE MRI sequence was tested in 54 patients with SSc, showed high sensitivity (92.8%) and specificity (75.0%), and proved reliable in assessing ILD and the extent of ground-glass opacities in patients with SSc and ILD (72). LUS emerged as a safe and cheap imaging technique for the evaluation of ILD through the assessment of B-lines and pleural line alterations. Gargani *et al*. confirmed a very high sensitivity in detecting SSc-related ILD in 69 patients. In this study, B-lines were more numerous in patients with dcSSc and ATA. A cut-off value of >10 B-lines on the whole chest or >1 B-line on the postero-basal chest was proposed for the screening of SSc-ILD. Moreover, assessing only the postero-basal chest seemed effective at combining high sensitivity with a less time-consuming approach (73).

The use of bronchoalveolar lavage (BAL) for the assessment of ILD secondary to SSc remains controversial. In a retrospective study on 68 SSc patients, a high percentage of neutrophils in FBAL-3 was significantly associated with the development of end-stage ILD (74).

Bronchiectasis in SSc may be caused by aspiration related to oesophageal dysmotility, to the use of immunosuppressant therapy, and to the direct effect of collagen deposition on airway diameter. Results from the Australian Scleroderma Cohort Study reported that 16.4% and 95.7% out of 256 patients had bronchiectasis and oesophageal dysmotility, respectively. A negative association between bronchiectasis and ILD was observed (75). Ostojic *et al*. reported the presence of small airway obstruction in 66.6% of SSc patients. HRCT patterns of ILD were found more frequently in patients with small airway obstruction and decreased lung diffusing capacity, indicating a possible prominent bronchiolar involvement in SSc-ILD (76).

In a multi-centric retrospective cohort study on 210 patients with SSc, cumulative occupational exposure to toxicants seemed to predict decline of FVC (≥ 10% from baseline) over time in SSc independently of gender (77).

Gastrointestinal involvement

The oesophagus is the most affected GI organ with up to 50–80% of patients having dysmotility or gastroesophageal reflux disease (GERD). The impaired lower oesophageal sphincter (LES) function and the altered oesophageal clearance leads to significant reflux. A study on 172 women with SSc who underwent esophagogastroduodenoscopy (EGDS) and high-resolution manometry reported a prevalence of Barrett's oesophagus of 12.8%. These women were significantly more likely to have absent contractility with hypotensive LES findings on high-resolution manometry (78).

Oesophageal dilation (defined as >10-mm diameter on coronal HRCT images) in patients with SSc is associated with dysmotility. The presence of oesophageal dysfunction is a poor prognostic indicator in SSc due to its impact on pulmonary disease through reflux, aspiration, and lung fibrosis. Wangkaew *et al*. reported that a worsening of oesophageal dilation predicted progression of lung fibrosis determined by HRCT score at 1-year follow-up in early SSc-ILD patients (79). To determine the effect of oesophageal dilation on SSc-ILD progression, Showalter *et al*. examined a cohort of 138 patients with SSc who had undergone HRCT and serial PFT, reporting that oesophageal dilation on axial chest HRCT was associated with a minimal and clinically insignificant decline in DLco, without any change in FVC during a 5-year follow-up period (80). A comprehensive assessment of oesophageal motility on 32 SSc patients applying high-resolution manometry and functional luminal imaging probe Panometry showed that both primary peristalsis and secondary peristalsis were heterogeneous in SSc. It was proposed that a complementary approach of evaluating primary peristalsis with high-resolution manometry and secondary peristalsis with Functional luminal imaging probe Panometry facilitated the characterisation of oesophageal function in SSc (81). In a study on 130 SSc patients, the presence of oesophageal dysmotility was associated with abnormal DLco (82).

Transabdominal oesophageal ultrasound was tested in a pilot study on 38 SSc. Abdominal oesophagus length was significantly shorter, whereas the gastro-oesophageal angle and the angle change before and after drinking water were larger in the SSc group. Abdominal oesophagus length was negatively correlated with larger oesophagus diameters (83).

Recently, a prospective cohort of SSc patients with GI symptoms completed a scintigraphy-based whole gut transit study. Among the 100 enrolled patients, 48% had slow colonic transit. After a multivariate analysis, the association between slow colonic transit and telangiectasia and less restrictive lung disease on PFTs remained statistically significant (84).

GI tract involvement may lead to malnutrition, however, its prevalence in SSc

was found to be lower than expected in a study on 102 SSc patients (85).
Karalilova *et al*. reported significantly higher spleen stiffness in 34 SSc patients especially with dcSSc. Their study showed that ultrasound elastography was a reliable and easy-to-implement method for detecting early fibrous changes in the spleen of SSc patients (86).
Although rare, primary biliary cholangitis (PBC) is the leading cause of liver disease in SSc. Patients with PBC had more limited forms of SSc and were less frequently affected by ILD but required early initiation of treatment with ursodeoxycholic acid to prevent cirrhosis (87).

COVID-19 and SSc
The COVID-19 pandemic affected the management of SSc-ILD. The striking radiological similarities between the two diseases make it difficult to distinguish a worsening of SSc-ILD from a COVID-19 superinfection (88). Orlandi *et al*. showed that the presence of consolidations in the lower lobes remained independently associated with COVID-19 pneumonia, whereas signs of fibrosis in ground-glass opacities in the lower lobes remained independently associated with SSc-ILD (89).

Take home messages
- Nailfold videocapillaroscopy (NVC), laser speckle contrast analysis (LASCA) and digital thermal monitoring may distinguish different vascular phenotypes of SSc (29-31).
- An active screening programme for PAH may improve survival and reduce the annual rate of hospital readmissions of SSc patients (37).
- Patients with SSc are at higher risk for diastolic dysfunction, myocardial fibrosis, arrhythmias, and moderate/severe valvulopathy (44, 46, 48-50).
- Positive RF, ACPA, and anti-CarP antibodies were associated with different musculoskeletal comorbidities in SSc patients (51).
- High-frequency ultrasound allows objective assessment of cutaneous fibrosis and detection of subclinical abnormalities of the skin and may be preferably employed in clinical trials as opposed to mRSS (54).
- African American ethnicity is independently associated with a higher risk for SRC and a higher prevalence of anti-Ro antibodies (62).
- Radiomics and lung ultrasound (LUS) are precise, sensitive, and specific tools able to improve the detection and the characterisation of SSc-ILD severity (65, 66, 72, 73).
- The extent of oesophageal dilation may predict the rate of progression of lung fibrosis in SSc patients (79).

Treatment
A combination therapy approach should be considered to target different pathways at the same time. The identification of new pathogenetic inflammatory and fibrotic pathways led to the approval of new drugs, such as tocilizumab and nintedanib (1).

Interstitial lung disease and pulmonary hypertension
The efficacy of CYC in the SSc-ILD treatment has been largely recognised. Yilmaz *et al*. compared the effectiveness of CYC to that of rituximab (RTX) in a study on 61 patients. RTX may be more effective than CYC at relieving cough, DUs, dysphagia, diarrhoea and RP. A significant increase in forced vital capacity (FVC) was observed in patients treated with CYC but not in the RTX group (90).
Recent data from the phase 3 Safety and Efficacy of Nintedanib in SSc (SENSCIS) reported that Nintedanib, an intracellular inhibitor of tyrosine kinase, slowed the progression of SSc-ILD (91). Another post-hoc analysis from the SENSCIS trial compared patients treated with nintedanib to those taking placebo and confirmed the higher percentage of patients exhibiting decline in FVC% predicted in the placebo group corroborating the effectiveness of nintedanib in SSc-ILD (92). Kuwana *et al*. confirmed its effectiveness both in the Japanese and in the non-Japanese population (93).
Tocilizumab showed promising results in the treatment of ILD in patients with early dcSSc. A recent analysis of patients enrolled in the focuSSced trial aimed to evaluate the effectiveness of tocilizumab on FVC and quantitative HRCT assessment compared to placebo. Out of 210 patients, 136 patients had ILD at baseline and in most cases, it was moderate or severe (>10% lung involvement). As expected, patients with greater quantitative ILD and quantitative lung fibrosis had a lower % predicted FVC, and patients treated with Tocilizumab showed a better preservation of FVC over 48 weeks compared to the placebo group (94).

Skin and musculoskeletal involvement
Karalilova *et al*. evaluated the efficacy of tofacitinib, a JAK1/JAK3 inhibitor, compared to methotrexate (MTX) on skin and musculoskeletal involvement in SSc patients. Data from this study revealed a significantly lower ultrasound skin thickness and a significant reduction of mRSS mean change and mean percent change at 26 and 52 weeks in patients treated with Tofacitinib (95). You *et al*. showed that patients treated with tofacitinib had a significant decrease in mRSS and a shorter response time than the control group (96). Agostini *et al*. reported a significant decrease in mRSS at 6 months of follow-up and a stabilisation after one year in 24 patients with refractory dcSSc treated with immunoglobulins (IVIg) (97). Perkovic *et al*. recently reported complete resolution of DUs, a reduction in mRSS, and an improvement of DLco in a population of SSc patients after adding IVIg to CYC (98).

Gastrointestinal involvement
A study involving 65 SSc patients suggested polidocanol injections as a useful and possible treatment for SSc-related small-bowel angioectasia (99). Hii et al. reported a significant improvement of heartburn in SSc patients with GERD at 3 months, and at 1 and 3 years after partial fundoplication (100).

Vascular involvement
The management of DUs in SSc requires a multidisciplinary approach and includes local wound bed treatment together with systemic drugs (101). In a multi-centric prospective study on 63 SSc patients, endothelin receptor antagonists (ERA) were more effective at reducing the appearance of new DUs com-

pared to phosphodiesterase type 5 inhibitors (PDEis), showing a similar time for DU healing (102). Botulinum toxin (BTX-A) may be effective in the treatment of RP and DUs (103). Shenavandeh *et al*. compared the effectiveness of BTX-A injection to iloprost and alprostadil; both groups (95.5% in the BTX-A population and 90.5% in the prostaglandin one) experienced a healing of DUs and a significant decrease in pain (104). Data from a retrospective study on 47 patients with SSc reported a worse tolerability and a higher dropout rate for the daily scheme compared to the continuous outpatient protocol (105).

Other treatments and future perspectives

An improvement of hands function with Maitland's joint mobilisation and therapeutic exercises was recently reported by a study on 24 patients (106). Waszczykowski *et al*. showed a significant improvement in hand function and in pain in 27 patients treated with supervised rehabilitation compared to 24 controls that performed a home exercise programme (107). Hesselstrand *et al*. conducted a multi-centric study on treatment with Paquinimod on 9 SSc patients with rapidly progressive disease, and showed a mild reduction of myofibroblasts in skin biopsies (108).

Take home messages

- Rituximab, nintedanib and cyclophosphamide are effective in the management of SSc-ILD by slowing the progression rate (90-92).
- Recent studies reported a more significant decrease in mRSS in patients treated with tofacitinib (95, 96). Intravenous immunoglobulins (IVIg) provide promising results in the treatment of skin involvement (97, 98).
- Fundoplication is an effective surgical approach in SSc patients with GERD refractory to pharmacological therapy (100).
- Treatment of DUs requires a multidisciplinary approach with specialised nursing. Botulinum toxin (BTX-A) and prostanoids were equally effective at managing ischaemic DUs (104).
- Supervised rehabilitation therapy is essential for the improvement of hand motility and pain (106, 107).

Patient-reported outcomes (PROs)

A very important step forward in PRO evaluation in SSc has been made with the development and validation of a SSc-specific questionnaire, called the EULAR SSc Impact of Disease (ScleroID), in a multicentric project involving 11 European expert SSc centres. Ten health dimensions with the highest ranking were selected, and each of them was assigned a weight following patient assessment. The experts translated each health dimension into one question with Numeric Rating Scales (NRS); these questions formed the final ScleroID questionnaire, which was validated in a cross-sectional international validation cohort study performed on 472 patients. The validation study showed a better sensitivity to change over a mean follow-up of 12.2 months than comparators such as Short Form-36 (SF-36), EuroQol Five Dimensional (EQ-5D), and the SSc-Health Assessment Questionnaire (HAQ). The ScleroID questionnaire proved easy to apply, had high internal consistency, and showed good correlation with the patient global assessment (109).

Take home message

- The ScleroID questionnaire is a new, SSc-specific, and patient-derived PRO measure which has proven superior to comparators and is thus suitable for clinical use (109).

Conclusions

This review provides some innovative studies published in 2021. Substantial progress was made in the understanding of SSc pathogenesis, clinical manifestations, and therapy. Only a comprehensive knowledge of SSc will allow to refine the prognostic stratification of SSc patients, and thus a better prediction of the clinical outcome and rate of progression for each patient.

Take home messages

- SSc is a challenging disease, with prominent cardiovascular and lung impairment, variable onset and course, and highly heterogeneous clinical presentation, with conspicuous healthcare costs (1, 24).
- The effort of clinicians should be aimed at the early diagnosis to target clinical manifestations when still reversible (17).
- Novel protocols for old medications and promising new treatments are emerging (90-92, 94-98, 108).
- Growing interest is raising towards non-pharmacological treatments, such as rehabilitation interventions (106, 107).

References

1. LESCOAT A, VARGA J, MATUCCI-CERINIC M, KHANNA D: New promising drugs for the treatment of systemic sclerosis: pathogenic considerations, enhanced classifications, and personalized medicine. *Expert Opin Investig Drugs* 2021; 30(6): 635-52. https://doi.org/10.1080/13543784.2021.1923693
2. DI BATTISTA M, BARSOTTI S, ORLANDI M *et al*.: One year in review 2021: systemic sclerosis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 131): S3-12. https://doi.org/10.55563/clinexprheumatol/izadb8
3. ORLANDI M, LEPRI G, DAMIANI A *et al*.: One year in review 2020: systemic sclerosis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 125): S3-17.
4. CLARK KEN, CAMPOCHIARO C, CSOMOR E *et al*.: Molecular basis for clinical diversity between autoantibody subsets in diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2021; 80(12): 1584-93. http://dx.doi.org/10.1136/annrheumdis-2021-220402
5. ABIGNANO G, HERMES H, PIERA-VELAZQUEZ S, ADDYA S, DEL GALDO F, JIMENEZ SA: Global gene expression analysis of systemic sclerosis myofibroblasts demonstrates a marked increase in the expression of multiple NBPF genes. *Sci Rep* 2021; 11(1): 20435. https://doi.org/10.1038/s41598-021-99292-y
6. KOBAYASHI S, NAGAFUCHI Y, OKUBO M *et al*.: Integrated bulk and single-cell RNA-sequencing identified disease-relevant monocytes and a gene network module underlying systemic sclerosis. *J Autoimmun* 2021; 116: 102547. https://doi.org/10.1016/j.jaut.2020.102547
7. HERNANDEZ-GONZALEZ I, TENORIO-CASTANO J, OCHOA-PARRA N *et al*.: Novel genetic and molecular pathways in pulmonary arterial hypertension associated with connective tissue disease. *Cells* 2021; 10(6): 1488. https://doi.org/10.3390/cells10061488
8. ROMANO E, ROSA I, FIORETTO BS *et al*.: a candidate gene study reveals association between a variant of the SRp55 splicing factor gene and systemic sclerosis. *Clin Exp Rheumatol* 2022; 40(10): 1922-26. https://doi.org/10.55563/clinexprheumatol/mpgq0y
9. KERICK M, GONZÁLEZ-SERNA D, CARNERO-MONTORO E *et al*.: Expression quantitative trait locus analysis in systemic sclero-

sis identifies new candidate genes associated with multiple aspects of disease pathology. *Arthritis Rheumatol* 2021; 73(7): 1288-300. https://doi.org/10.1002/art.41657
10. BOSSINI-CASTILLO L, VILLANUEVA-MARTIN G, KERICK M *et al*.: Genomic Risk Score impact on susceptibility to systemic sclerosis. *Ann Rheum Dis* 2021; 80(1): 118-27. http://doi.org/10.1136/annrheumdis-2020-218558
11. ZEHENDER A, LI YN, LIN NY *et al*.: TGFβ promotes fibrosis by MYST1-dependent epigenetic regulation of autophagy. *Nat Commun* 2021; 12(1): 4404. https://doi.org/10.1038/s41467-021-24601-y
12. ANDREUCCI E, MARGHERI F, PEPPICELLI S *et al*.: Glycolysis-derived acidic microenvironment as a driver of endothelial dysfunction in systemic sclerosis. *Rheumatology* (Oxford) 2021; 60(10): 4508-19. https://doi.org/10.1093/rheumatology/keab022
13. RUDNIK M, HUKARA A, KOCHEROVA I *et al*.: Elevated fibronectin levels in profibrotic CD14+ monocytes and CD14+ macrophages in systemic sclerosis. *Front Immunol* 2021; 12: 642891. https://doi.org/10.3389/fimmu.2021.642891
14. RUDNIK M, ROLSKI F, JORDAN S *et al*.: Regulation of monocyte adhesion and type I interferon signaling by CD52 in patients with systemic sclerosis. *Arthritis Rheumatol* (Hoboken) 2021; 73(9): 1720-30. https://doi.org/10.1002/art.41737
15. KUZUMI A, YOSHIZAKI A, MATSUDA KM *et al*.: Interleukin-31 promotes fibrosis and T helper 2 polarization in systemic sclerosis. *Nat Commun* 2021; 12(1): 5947. https://doi.org/10.1038/s41467-021-26099-w
16. LAURENT P, ALLARD B, MANICKI P *et al*.: TGFβ promotes low IL10-producing ILC2 with profibrotic ability involved in skin fibrosis in systemic sclerosis. *Ann Rheum Dis* 2021; 80(12): 1594-603. https://doi.org/10.1136/annrheumdis-2020-219748
17. JOHNSON SR, VAN DEN HOOGEN F, DEVAKANDAN K, MATUCCI-CERINIC M, POPE JE: Systemic sclerosis: To subset or not to subset, that is the question. *Eur J Rheumatol* 2020; 7 (Suppl. 3): S222-7. https://doi.org/10.5152/eurjrheum.2020.19116
18. DE ANGELIS R, GIUGGIOLI D, BAJOCCHI G *et al*.: Sex-related differences in systemic sclerosis: a multicenter cross-sectional study from the National Registry of the Italian Society for Rheumatology. *J Rheumatol* 2022; 49(2): 176-85. https://doi.org/10.3899/jrheum.210794
19. LAZZARONI MG, MARASCO E, CAMPOCHIARO C *et al*.: The clinical phenotype of systemic sclerosis patients with anti-PM/Scl antibodies: results from the EUSTAR cohort. *Rheumatology* (Oxford) 2021; 60(11): 5028-41. https://doi.org/10.1093/rheumatology/keab152
20. DE ALMEIDA CHAVES S, POREL T, MOUNIÉ M *et al*.: Sine scleroderma, limited cutaneous, and diffused cutaneous systemic sclerosis survival and predictors of mortality. *Arthritis Res Ther* 2021; 23(1): 295. https://doi.org/10.1186/s13075-021-02672-y
21. LESCOAT A, MURPHY SL, CHEN YT *et al*.: Symptom experience of limited cutaneous systemic sclerosis from the patients' perspective: A qualitative study. *Semin Arthritis Rheum* 2022; 52: 151926. https://doi.org/10.1016/j.semarthrit.2021.11.003
22. WOJECK RK, SILVA SG, BAILEY DE JR *et al*.: Pain and self-efficacy among patients with systemic sclerosis: a Scleroderma Patient-Centered Intervention Network Cohort Study. *Nurs Res* 2021; 70(5): 334-43. https://doi.org/ https://doi.org/10.1097/nnr.0000000000000528
23. VAN LEEUWEN NM, CIAFFI J, LIEM SIE, HUIZINGA TWJ, DE VRIES-BOUWSTRA JK: Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants. *Rheumatology* (Oxford) 2021; 60(8): 3646-55. https://doi.org/10.1093/rheumatology/keaa827
24. KHANNA D, FURST D, LI J *et al*.: Economic and healthcare resource use burden of systemic sclerosis [abstract]. *Arthritis Rheumatol* 2021; 73 (Suppl 9).
25. MARTIN CALDERON L, CHAUDHURY M, POPE JE: Healthcare utilization and economic burden in systemic sclerosis: a systematic review. *Rheumatology* (Oxford) 2022; 61(8): 3123-31. https://doi.org/10.1093/rheumatology/keab847
26. HUGHES M, ZANATTA E, SANDLER RD, AVOUAC J, ALLANORE Y: Improvement with time of vascular outcomes in systemic sclerosis: a systematic review and meta-analysis study. *Rheumatology* (Oxford) 2022; 61(7): 2755-69. https://doi.org/10.1093/rheumatology/keab850
27. BADAK SO, GULEK B, KAYACAN ERDOGAN E, BINOKAY H, ERKEN E: Arterial evaluation of systemic sclerosis patients with Doppler ultrasound: What did we find? *Int J Rheum* Dis 2021; 24(7): 954-62. https://doi.org/10.1111/1756-185X.14158
28. AVENATTI E, BRUNO G, PRIORA M *et al*.: Cardiovascular organ damage in clinical subtypes of systemic sclerosis: arterial stiffness and echocardiography might not be the ideal tools for patient risk stratification. *Cardiol Res Pract* 2021; 2021: 7915890. https://doi.org/10.1155/2021/7915890
29. THOMAS JK, RADIC M, TUCKER JR, OVERBURY R, FRECH TM: Raynaud phenomenon in systemic sclerosis: does digital thermal monitoring correlate to specific nailfold videocapillaroscopy abnormalities? *J Rheumatol* 2021; 48(2): 247-50. https://doi.org/10.3899/jrheum.191371
30. FRECH TM, OU Z, PRESSON AP: Clinical bedside tools to assess systemic sclerosis vasculopathy: can digital thermal monitoring and sublingual microscopy identify patients with digital ulcers? *J Rheumatol* 2021; 48(10): 1566-8. https://doi.org/10.3899/jrheum.201234
31. GIGANTE A, VILLA A, ROSATO E: Laser speckle contrast analysis predicts major vascular complications and mortality of patients with systemic sclerosis. *Rheumatology* (Oxford) 2021; 60(4): 1850-7. https://doi.org/10.1093/rheumatology/keaa514
32. PAGKOPOULOU E, SOULAIDOPOULOS S, TRIANTAFYLLIDOU E *et al*.: Peripheral microcirculatory abnormalities are associated with cardiovascular risk in systemic sclerosis: a nailfold video capillaroscopy study. *Clin Rheumatol* 2021; 40(12): 4957-68. https://doi.org/10.1007/s10067-021-05795-4
33. CASSIUS C, SETA V, MONFORT JB *et al*.: Systemic sclerosis is associated with lower limb vascular stiffness and microvascular impairment: results from a prospective study. *Clin Rheumatol* 2021; 40(9): 3679-86. https://doi.org/10.1007/s10067-021-05672-0
34. RUBIO-RIVAS M, HOMS NA, CUARTERO D, CORBELLA X: The prevalence and incidence rate of pulmonary arterial hypertension in systemic sclerosis: Systematic review and meta-analysis. *Autoimmun Rev* 2021; 20(1): 102713. https://doi.org/10.1016/j.autrev.2020.102713
35. RUARO B, SALTON F, BARATELLA E *et al*.: An overview of different techniques for improving the treatment of pulmonary hypertension secondary in systemic sclerosis patients. *Diagnostics* (Basel) 2022; 12(3): 616. https://doi.org/10.3390/diagnostics12030616
36. YOUNG A, MOLES VM, JAAFAR S *et al*.: Performance of the DETECT algorithm for pulmonary hypertension screening in a systemic sclerosis cohort. *Arthritis Rheumatol* 2021; 73(9): 1731-7. https://doi.org/10.1002/art.41732
37. SHOWALTER K, PINHEIRO LC, JANNATKHAH D *et al*.: Hospital readmission in systemic sclerosis associated pulmonary hypertension: Results from the PHAROS registry. *Rheumatology* (Oxford) 2022; 61(4): 1510-7. https://doi.org/10.1093/rheumatology/keab569
38. TONA F, ZANATTA E, MONTISCI R *et al*.: Higher ventricular-arterial coupling derived from three-dimensional echocardiography is associated with a worse clinical outcome in systemic sclerosis. *Pharmaceuticals* (Basel) 2021; 14(7): 646. https://doi.org/10.3390/ph14070646
39. MUKHERJEE M, MERCURIO V, HSU S *et al*.: Assessment of right ventricular reserve utilizing exercise provocation in systemic sclerosis. *Int J Cardiovasc Imaging* 2021; 37(7): 2137-47. https://doi.org/10.1007/s10554-021-02237-9
40. NINAGAWA K, KATO M, OHIRA H *et al*.: The assessment of left heart disease in patients with systemic sclerosis and pulmonary hypertension. *Clin Exp Rheumatol* 2021; 39 (Suppl. 131): S103-10. https://doi.org/10.55563/clinexprheumatol/c1j9gb
41. DUMITRU RB, BISSELL LA, ERHAYIEM B *et al*.: Predictors of subclinical systemic sclerosis primary heart involvement characterised by microvasculopathy and myocardial fibrosis. *Rheumatology* (Oxford) 2021; 60(6) 2934-45. https://doi.org/10.1093/rheumatology/keaa742
42. LUI JK, SANGANI RA, CHEN CA *et al*.: The prognostic value of cardiac axis deviation in systemic sclerosis-related pulmonary hypertension. *Arthritis Care Res* (Hoboken) 2022; 74(7): 1219-26. https://doi.org/10.1002/acr.24724
43. HINZE AM, PERIN J, WOODS A *et al*.: Diastolic dysfunction in systemic sclerosis: risk factors and impact on mortality. *Arthritis Rheumatol* 2022; 74(5): 849-59. https://doi.org/10.1002/art.42054
44. FONTES OLIVEIRA M, REI AL, OLIVEIRA

MI, ALMEIDA I, SANTOS M: Prevalence and prognostic significance of heart failure with preserved ejection fraction in systemic sclerosis. *Future Cardiol* 2022; 18(1): 17-25. https://doi.org/10.2217/fca-2020-0238
45. DUMITRU RB, BISSELL LA, ERHAYIEM B *et al*.: Cardiovascular outcomes in systemic sclerosis with abnormal cardiovascular MRI and serum cardiac biomarkers. *RMD Open* 2021; 7(3): e001689. https://doi.org/10.1136/rmdopen-2021-001689
46. HUI M, ZHOU J, ZHANG L *et al*.: Prevalence and risk factors for left ventricular diastolic dysfunction in systemic sclerosis: a multicenter study of CRDC cohort in China. *Clin Rheumatol* 2021; 40(11): 4589-96. https://doi.org/10.1007/s10067-021-05804-6
47. CAFORIO ALP, DE LUCA G, BARITUSSIO A *et al*.: Serum organ-specific anti-heart and anti-intercalated disk autoantibodies as new autoimmune markers of cardiac involvement in systemic sclerosis: frequency, clinical and prognostic correlates. *Diagnostics* (Basel) 2021; 11(11): 2165. https://doi.org/10.3390/diagnostics11112165
48. JIANG X, ZHANG F, LI Y *et al*.: Clinical assessment of cardiac impairment favored by two-dimensional speckle tracking echocardiology in patients with systemic sclerosis. *Rheumatology* (Oxford) 2022; 61(6): 2432-40. https://doi.org/10.1093/rheumatology/keab724
49. KURMANN RD, EL-AM EA, RADWAN YA *et al*:. Increased risk of valvular heart disease in systemic sclerosis: an underrecognized cardiac complication. *J Rheumatol* 2021; 48(7): 1047-52. https://doi.org/10.3899/jrheum.201005
50. NARVÁEZ J, LLUCH J, RUIZ-MAJORAL A, SÁNCHEZ-CORRAL MA, CLAVER E, NOLLA JM: Increased prevalence of moderate to severe mitral and aortic valve dysfunction in systemic sclerosis: a case-control study. *J Rheumatol* 2021; 48(3): 394-401. https://doi.org/10.3899/jrheum.201025
51. RICCARDI A, MARTINROCHE G, CONTINBORDES C *et al*.: Erosive arthritis autoantibodies in systemic sclerosis. *Semin Arthritis Rheum* 2022; 52: 151947. https://doi.org/10.1016/j.semarthrit.2021.11.013
52. SAKCHAIKUL A, CHOWCHUEN P, FOOCHAROEN C, THAMMAROJ P: Prevalence and clinical association with acro-osteolysis in early systemic sclerosis. *Clin Exp Rheumatol* 2021; 39(5): 1093-8. https://doi.org/10.55563/clinexprheumatol/vggbdq
53. FRECH TM, VANBUREN JM, STARTUP E *et al*.: Does hand involvement in systemic sclerosis limit completion of patient-reported outcome measures? *Clin Rheumatol* 2021; 40(3): 965-71. https://doi.org/10.1007/s10067-020-05467-9
54. MUKTABHANT C, THAMMAROJ P, CHOWCHUEN P, FOOCHAROEN C: Prevalence and clinical association with calcinosis cutis in early systemic sclerosis. *Mod Rheumatol* 2021; 31(6): 1113-9. https://doi.org/10.1080/14397595.2021.1886654
55. FAIRCHILD R, CHUNG M, SHARPLESS L, LI S, CHUNG L: Ultrasound detection of calcinosis and association with ulnar artery occlusion in patients with systemic sclerosis. *Arthritis Care Res* (Hoboken) 2021; 73(9): 1332-7. https://doi.org/10.1002/acr.24327
56. RAJA J, BALAIKERISNAN T, RAMANAIDU LP, GOH KJ: Large fiber peripheral neuropathy in systemic sclerosis: A prospective study using clinical and electrophysiological definition. *Int J Rheum Dis* 2021; 24(3): 347-54. https://doi.org/10.1002/acr.24327
57. MALTEZ N, CHOI MY, TROYANOV Y *et al*.: Canadian Scleroderma Research Group. Trigeminal neuralgia in systemic sclerosis. *Semin Arthritis Rheum* 2021; 51(1): 318-23. https://doi.org/10.1016/j.semarthrit.2021.01.001
58. LIN CY, SU YJ, CHENG TT *et al*.: Increased risk of end-stage renal disease in patients with systemic sclerosis. *Scand J Rheumatol* 2022; 51(2): 120-7. https://doi.org/10.1080/03009742.2021.1917143
59. GIGANTE A, HOFFMANN-VOLD AM, ALUNNI FEGATELLI D *et al*.: Estimated glomerular filtration rate is a marker of mortality in the European Scleroderma Trials and Research Group (EUSTAR) database. *Rheumatology* (Oxford) 2021; 61(1): 213-22. https://doi.org/10.1093/rheumatology/keab302
60. LEODORI G, PELLICANO C, GIGANTE A, ROSATO E: Estimated glomerular filtration rate and renal resistive index as possible predictive markers of mortality in systemic sclerosis. *Eur J Intern Med* 2021; 87: 83-9. https://doi.org/10.1016/j.ejim.2021.01.025
61. CIANCI R, GIGANTE A, BAGORDO D *et al*.: Renal resistive index in IgA nephropathy and renal scleroderma vasculopathy. *Microvasc Res* 2021; 133: 104095. https://doi.org/10.1016/j.mvr.2020.104095
62. FORMAN CJ, OLSON SW, GORDON SM *et al*.: Association of race and risk of future scleroderma renal crisis at systemic sclerosis diagnosis. *Arthritis Care Res* (Hoboken) 2021 Nov 4. https://doi.org/10.1002/acr.24807
63. HOFFMANN-VOLD AM, MAHER TM, PHILPOT EE, ASHRAFZADEH A, DISTLER O: Assessment of recent evidence for the management of patients with systemic sclerosis-associated interstitial lung disease: a systematic review. *ERJ Open Res* 2021; 7(1): 00235-2020. https://doi.org/10.1183/23120541.00235-2020
64. LANDINI N, ORLANDI M, BRUNI C *et al*.: Computed tomography predictors of mortality or disease progression in systemic sclerosis-interstitial lung disease: a systematic review. *Front Med* (Lausanne) 2022; 8: 807982. https://doi.org/10.3389/fmed.2021.807982
65. SCHNIERING J, MACIUKIEWICZ M, GABRYS HS *et al*.: Computed tomography-based radiomics decodes prognostic and molecular differences in interstitial lung disease related to systemic sclerosis. *Eur Respir J* 2022; 59(5): 2004503. https://doi.org/10.1183/13993003.04503-2020
66. MARTINI K, BAESSLER B, BOGOWICZ M *et al*.: Applicability of radiomics in interstitial lung disease associated with systemic sclerosis: proof of concept. *Eur Radiol* 2021; 31(4): 1987-98. https://doi.org/10.1007/s00330-020-07293-8
67. TEMIZ KARADAG D, CAKIR O, KOMAC A, YAZICI A, CEFLE A: Software-based quantitative analysis of lung parenchyma in patients with systemic sclerosis may provide new generation data for pulmonary fibrosis. *Int J Clin Pract* 2021; 75(4): e13931. https://doi.org/10.1111/ijcp.13931
68. TEMIZ KARADAG D, CAKIR O, SAN S, YAZICI A, CIFTCI E, CEFLE A: Association of quantitative computed tomography ındices with lung function and extent of pulmonary fibrosis in patients with systemic sclerosis. *Clin Rheumatol* 2022; 41(2): 513-21. https://doi.org/10.1007/s10067-021-05918-x
69. CARNEVALE A, SILVA M, MAIETTI E *et al*.: Longitudinal change during follow-up of systemic sclerosis: correlation between high-resolution computed tomography and pulmonary function tests. *Clin Rheumatol* 2021; 40(1): 213-9. https://doi.org/10.1007/s10067-020-05375-y
70. ROOFEH D, BARRATT SL, WELLS AU *et al*.: Outcome measurement instrument selection for lung physiology in systemic sclerosis associated interstitial lung disease: A systematic review using the OMERACT filter 2.1 process. *Semin Arthritis Rheum* 2021; 51(6): 1331-41. https://doi.org/10.1016/j.semarthrit.2021.08.001
71. ORLANDI M, LANDINI N, CERINIC MM, COLAGRANDE S: Pulmonary magnetic resonance imaging in systemic sclerosis: a jump in the future to unravel inflammation in interstitial lung disease. *Clin Rheumatol* 2021; 40(9): 3461-4. https://doi.org/10.1007/s10067-021-05869-3
72. LANDINI N, ORLANDI M, OCCHIPINTI M *et al*.: Ultrashort echo-time magnetic resonance imaging sequence in the assessment of systemic sclerosis-interstitial lung disease. *J Thorac Imaging* 2022 Feb 4. https://doi.org/10.1097/rti.0000000000000637
73. GARGANI L, ROMEI C, BRUNI C *et al*.: Lung ultrasound B-lines in systemic sclerosis: cut-off values and methodological indications for interstitial lung disease screening. *Rheumatology* (Oxford) 2022; 61(SI): SI56-SI64. https://doi.org/10.1093/rheumatology/keab801
74. KASE K, WATANABE S, SAEKI K *et al*.: Fractional analysis of bronchoalveolar lavage in systemic sclerosis-associated interstitial lung disease. *J Thorac Dis* 2021; 13(7): 4146-55. https://doi.org/10.21037/jtd-20-2596
75. SMITH R, HARRISON M, LAM KV *et al*.: The emerging association between bronchiectasis and systemic sclerosis: assessing prevalence and potential causality. *Intern Med J* 2021 Dec 11. https://doi.org/10.1111/imj.15661
76. OSTOJIC P, VUJOVIC M: Prevalence and clinical correlates of small airway obstruction in patients with systemic sclerosis. *Clin Rheumatol* 2021; 40(4): 1417-22. https://doi.org/10.1007/s10067-020-05353-4
77. THOREAU B, EUSTACHE M, FIEVET A, LASFARGUES G, PLANTIER L, DIOT E: Independent association between occupational exposure and decline of FVC in systemic sclerosis: a multicenter recruitment retrospective cohort study. *Chest* 2022; 161(4): 1011-21. https://doi.org/10.1016/j.chest.2021.11.009
78. SNYDER DL, CROWELL MD, KAHN A, GRIFFING WL, UMAR S, RAMIREZ FC:

Prevalence of Barrett's esophagus in female patients with scleroderma. *Am J Gastroenterol* 2021; 116(3): 517-21. https://doi.org/10.14309/ajg.0000000000001109

79. WANGKAEW S, LOSURIYA P, EUATHRONGCHIT J: Worsening of esophageal dilatation is associated with increase in a high-resolution computed tomography (HRCT) score in early systemic sclerosis-associated interstitial lung disease (SSc-ILD). *Clin Rheumatol* 2021; 40(3): 955-63. https://doi.org/10.1007/s10067-020-05346-3
80. SHOWALTER K, HOFFMANN A, RICHARDSON C *et al*.: Esophageal dilation and other clinical factors associated with pulmonary function decline in patients with systemic sclerosis. *J Rheumatol* 2021; 48(12): 1830-8. https://doi.org/10.3899/jrheum.210533
81. CARLSON DA, PRESCOTT JE, GERMOND E *et al*.: Heterogeneity of primary and secondary peristalsis in systemic sclerosis: a new model of "scleroderma esophagus". *Neurogastroenterol Motil* 2022; 34(7): e14284. https://doi.org/10.1111/nmo.14284
82. KUCHIPUDI N, KISHORE S, KUO CL, LAKSHMINARAYANAN S, MANDHADI R: Esophageal dysmotility and lung disease in patients with systemic sclerosis: is there a possible association or correlation? A retrospective chart review. *Rheumatol Int* 2021; 41(11): 1965-70. https://doi.org/10.1007/s00296-021-04880-w
83. MA L, ZHU Q, ZHANG Y *et al*.: Esophagus involvement in systemic sclerosis: ultrasound parameters and association with clinical manifestations. *Arthritis Res Ther* 2021; 23(1): 122. https://doi.org/10.1186/s13075-021-02505-y
84. CHEAH JX, PERIN J, VOLKMANN ER *et al*.: Slow colonic transit in systemic sclerosis: an objective assessment of risk factors and clinical phenotype. *Arthritis Care Res* (Hoboken) 2021 Aug 9. https://doi.org/10.1002/acr.24767
85. ROSATO E, GIGANTE A, GASPERINI ML, PROIETTI L, MUSCARITOLI M: Assessing malnutrition in systemic sclerosis with Global Leadership Initiative on Malnutrition and European Society of Clinical Nutrition and Metabolism Criteria. *JPEN J Parenter Enteral Nutr* 2021; 45(3): 618-24. https://doi.org/10.1002/jpen.1872
86. KARALILOVA R, DOYKOVA K, BATALOV Z, DOYKOV D, BATALOV A: Spleen elastography in patients with systemic sclerosis. *Rheumatol Int* 2021; 41(3): 633-41. https://doi.org/10.1007/s00296-020-04772-5
87. DAVID C, CHAIGNE B, HOLLANDE C *et al*.: Primary biliary cholangitis and systemic sclerosis (Reynolds syndrome): a case-control study. *Autoimmun Rev* 2021; 20(7): 102842. https://doi.org/10.1016/j.autrev.2021.102842
88. ORLANDI M, LANDINI N, BRUNI C, COLAGRANDE S, MATUCCI-CERINIC M, KUWANA M: Infection or autoimmunity? The clinical challenge of interstitial lung disease in systemic sclerosis during the COVID-19 Pandemic. *J Rheumatol* 2021; 48(5): 790-2. https://doi.org/10.3899/jrheum.200832
89. ORLANDI M, LANDINI N, SAMBATARO G *et al*.: The role of chest CT in deciphering interstitial lung involvement: systemic sclerosis versus COVID-19. *Rheumatology* (Oxford) 2022; 61(4): 1600-9. https://doi.org/10.1093/rheumatology/keab615
90. YILMAZ DD, BOREKCI S, MUSELLIM B: Comparison of the effectiveness of cyclophosphamide and rituximab treatment in patients with systemic sclerosis-related interstitial lung diseases: a retrospective, observational cohort study. *Clin Rheumatol* 2021; 40(10): 4071-9. https://doi.org/10.1007/s10067-021-05785-6
91. HIGHLAND KB, DISTLER O, KUWANA M *et al*.: 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* 2021; 9(1): 96-106. https://doi.org/10.1016/s2213-2600(20)30330-1
92. MAHER TM, MAYES MD, KREUTER M *et al*.: Effect of nintedanib on lung function in patients with systemic sclerosis-associated interstitial lung disease: further analyses of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2021; 73(4): 671-6. https://doi.org/10.1002/art.41576
93. KUWANA M, OGURA T, MAKINO S *et al*.: Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: a Japanese population analysis of the SENSCIS trial. *Mod Rheumatol* 2021; 31(1): 141-50. https://doi.org/10.1080/14397595.2020.1751402
94. ROOFEH D, LIN CJF, GOLDIN J *et al*.: Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol* 2021; 73(7): 1301-10. https://doi.org/10.1002/art.41668
95. KARALILOVA RV, BATALOV ZA, SAPUNDZHIEVA TL, MATUCCI-CERINIC M, BATALOV AZ: Tofacitinib in the treatment of skin and musculoskeletal involvement in patients with systemic sclerosis, evaluated by ultrasound. *Rheumatol Int* 2021; 41(10): 1743-53. https://doi.org/10.1007/s00296-021-04956-7
96. YOU H, XU D, HOU Y, ZHOU J, WANG Q, LI M, ZENG X: Tofacitinib as a possible treatment for skin thickening in diffuse cutaneous systemic sclerosis. *Rheumatology* (Oxford) 2021; 60(5): 2472-7. https://doi.org/10.1093/rheumatology/keaa613
97. AGOSTINI E, DE LUCA G, BRUNI C *et al*.: Intravenous immunoglobulins reduce skin thickness in systemic sclerosis: evidence from systematic literature review and from real life experience. *Autoimmun Rev* 2021; 20(12): 102981. https://doi.org/10.1016/j.autrev.2021.102981
98. PERKOVIĆ D, PETRIĆ M, BOŽIĆ I *et al*.: Low dose intravenous immunoglobulin in addition to cyclophosphamide in systemic sclerosis: single centre experience. *Wien Klin Wochenschr* 2021; 133(19-20): 1070-5. https://doi.org/10.1007/s00508-020-01669-y
99. IIO S, OKA S, SUMIOKA A, TSUBOI A *et al*.: Characteristics and treatment outcomes of small-bowel angioectasia in systemic sclerosis patients: a retrospective observational study. *Intern Med* 2022; 61(5): 615-22. https://doi.org/10.2169/internalmedicine.8034-21
100. HII A, LIU DS, KHOLMURODOVA F *et al*.: Partial fundoplication is effective treatment for female patients with gastroesophageal reflux and scleroderma: a multicenter comparative cohort study. *World J Surg* 2022; 46(1): 147-53. https://doi.org/10.1007/s00268-021-06326-7
101. HUGHES M, ALLANORE Y, EL AOUFY K *et al*.: A practical approach to the management of digital ulcers in patients with systemic sclerosis: a narrative review. *JAMA Dermatol* 2021; 157(7): 851-8. https://doi.org/10.1001/jamadermatol.2021.1463
102. CHANG SH, JUN JB, LEE YJ *et al*.: A clinical comparison of an endothelin receptor antagonist and phosphodiesterase type 5 inhibitors for treating digital ulcers of systemic sclerosis. *Rheumatology* (Oxford) 2021; 60(12): 5814-9. https://doi.org/10.1093/rheumatology/keab147
103. NAGARAJAN M, MCARTHUR P: Targeted high concentration botulinum toxin A injections in patients with Raynaud's phenomenon: a retrospective single-centre experience. *Rheumatol Int* 2021; 41(5): 943-9. https://doi.org/10.1007/s00296-020-04606-4
104. SHENAVANDEH S, SEPASKHAH M, DEHGHANI S, NAZARINIA M: A 4-week comparison of capillaroscopy changes, healing effect, and cost-effectiveness of botulinum toxin-A vs prostaglandin analog infusion in refractory digital ulcers in systemic sclerosis. *Clin Rheumatol* 2022; 41(1): 95-104. https://doi.org/10.1007/s10067-021-05900-7
105. BARSOTTI S, LORENZONI V, DI BATTISTA M *et al*.: Prostanoids in scleroderma microangiopathy: clinical and pharmacoeconomic comparison between two intravenous regimens. *Scand J Rheumatol* 2021; 50(4): 307-13. https://doi.org/10.1080/03009742.2020.1845395
106. SANTOS CARDOZO ROQUE LC, TENÓRIO ADS, DE AQUINO LT, FERREIRA RDS, DUARTE ALBP, DANTAS AT: Joint mobilization and therapeutic exercises in the hands of patients with systemic sclerosis: A preliminary randomized controlled trial. *Clin Rehabil* 2022; 36(1): 113-24. https://doi.org/10.1177/02692155211038728
107. WASZCZYKOWSKI M, DZIANKOWSKA-BARTKOWIAK B, PODGÓRSKI M, FABIŚ J, WASZCZYKOWSKA A: Role and effectiveness of complex and supervised rehabilitation on overall and hand function in systemic sclerosis patients – one-year follow-up study. *Sci Rep* 2021; 11(1): 15174. https://doi.org/10.1038/s41598-021-94549-y
108. HESSELSTRAND R, DISTLER JHW, RIEMEKASTEN G *et al*.: An open-label study to evaluate biomarkers and safety in systemic sclerosis patients treated with paquinimod. *Arthritis Res Ther* 2021; 23(1): 204. https://doi.org/10.1186/s13075-021-02573-0
109. BECKER MO, DOBROTA R, GARAIMAN A *et al*.: Development and validation of a patient-reported outcome measure for systemic sclerosis: the EULAR Systemic Sclerosis Impact of Disease (ScleroID) questionnaire. *Ann Rheum Dis* 2022; 81(4): 507-15. http://dx.doi.org/10.1136/annrheumdis-2021-220702