Patient subgroups and potential risk factors in systemic sclerosis: is there a possibility of an early diagnosis?

Systemic sclerosis is often well established at diagnosis, when the disease has already evolved to an obliterative vasculopathy with fibrosis and significant end-organ damage. The present classification criteria perform poorly when attempting to make an early diagnosis, limiting the possibility of early treatment and of preventing disease evolution and tissue damage, leading to loss of function and impairment of quality of life. Recently, experts have identified Raynaud's phenomenon, antinuclear antibodies and puffy fingers as 'red flags' that can be used as signs of suspected early systemic sclerosis. The positivity of other signs such as specific antibodies (anticentromere antibodies and anti-topoisomerase I) and capillaroscopy may allow a diagnosis of very early systemic sclerosis and prompt further investigation at the internal organ level. These red flags can help to track patients in the earliest phase of the disease and those at risk of progressing to overt disease. This 'window of opportunity' may allow treatment of the disease while it is still reversible when safe, efficacious and curative treatments will be available.

KEYWORDS: complications ■ early diagnosis ■ risk factors ■ systemic sclerosis

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Systemic sclerosis (SSc) is a chronic, connective tissue disease characterized by widespread fibrosis of the skin and internal organs, small-vessel vasculopathy and immune dysregulation with production of autoantibodies. The incidence of SSc is estimated to be between four and 20 new cases per 1,000,000 per year and the prevalence between 30 and 450 cases per 1,000,000 [1,2]. The prevalence of SSc was estimated to be 158 per 1,000,000 population in a French multiethnic group [3], and in the USA, it ranges across studies from three to 21 per 1,000,000 population [4]. SSc is characterized by a high level of clinical heterogeneity, an unpredictable course, high mortality and resistance to therapy [5]. For this reason it is considered to be one of the greatest challenges in the management of rheumatic diseases.

Diagnostic and therapeutic standards vary widely across the global clinical community, and no consensus has been reached on the optimum approach to screening and diagnosis [6]. The evaluation of patients with SSc should include assessments of the severity of each organ involvement, of functional impairments and of the impact on quality of life (QOL).

Although many classification schemes have been developed, all of them distinguish between the limited cutaneous disease, in which the skin lesions do not extend beyond the elbows and knees but may involve the face, and the diffuse cutaneous disease, which affects the thighs, arms and trunk.

Indeed, SSc is diagnosed according to the American College of Rheumatology classification criteria, which require either the presence of skin sclerosis proximal to metacarpophalangeal or metatarsophalangeal joints, or the presence of two out of three secondary criteria (sclerodactyly, digital ulcers or lung fibrosis) [7]. In order to overcome the limitations of the American College of Rheumatology criteria, LeRoy and others formulated criteria for limited forms of SSc, which basically define a group of pre-SSc [8]. According to the LeRoy criteria, patients with limited SSc must have Raynaud's phenomenon (RP) plus scleroderma-type nailfold capillary changes and/or autoantibodies [9].

Early diagnosis of SSc: is it possible?

Systemic sclerosis is easy to diagnose when the disease has already evolved to an obliterative vasculopathy with fibrosis and significant end-organ damage, but the present classification criteria [7,10] perform poorly for an early diagnosis [11–13]. This limits the possibility of early treatment and the prevention of disease evolution and tissue damage, leading to a loss of function and impairment of QOL. In fact, SSc is a disabling disease substantially decreasing patients daily function and QOL. Moreover, because of changes in the patient's appearance due to skin sclerosis, muscle atrophy and joint contracture, it also has a substantial impact on the patient's emotional and psychological wellbeing [14,15].

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Early stages of SSc are clinically characterized by the onset of RP (Figure 1), sclerodactyly and often by the presence of SSc-specific autoantibodies [9].

Almost all early SSc patients present an altered microvascular pattern at nailfold capillaroscopy [16]. The presence of an abnormal nailfold microvascular profile on capillaroscopy in patients with isolated RP predicts future evolution into a connective tissue disease [9]. In the early phase, signs of the disease are mainly puffy fingers (Figure 2) and/or a dysfunctional lower esophageal sphincter. However, any one of these early disease features are not specific for SSc, as other entities may also display a combination of these characteristics. At this point, doctors face two challenges:

- To confirm that a patient with these features is already affected by SSc – or at least a condition within the scleroderma spectrum: 'prescleroderma', [17] undifferentiated connective tissue disease [18] or mixed connective tissue disease [19];
- To decide how to treat this patient – aggressively or wait and stand by. In reality, these decisions are compromised by a lack of agreement and validation of criteria to define early disease, and a lack of adequate clinical trials targeting patients when they still have early 'prescleroderma tous' disease.

It has been proposed that early SSc could be defined as a state characterized by 'red flags' such as RP, antinuclear antibody (ANA) positivity, puffy fingers, disease-specific autoantibodies and capillarosopic microvascular alterations, as reported in Box 1 [20].

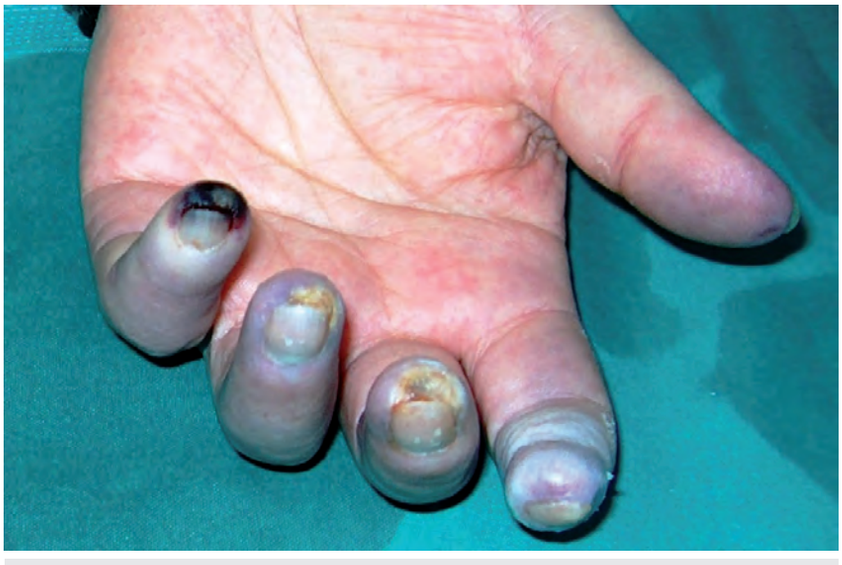

Figure 1. Raynaud's phenomenon and digital ulcers.

A Canadian register on 359 patients showed that the delay before diagnosis is 6.1 years after the onset of RP and 2.7 years after the onset of extra-RP symptoms [21]. This large gap between symptoms and diagnosis, which is mainly based on dermal fibrosis, could be regarded as a 'window of opportunity'. A very early diagnosis may allow us to treat the disease while it is still reversible through the appropriate treatment.

Although patients with RP, autoantibodies and SSc capillaroscopic pattern could be easily followed up, we still lack an agreement on the predictors that may allow us to understand which patients will progress to an established disease. For this reason patients must be followed up regularly even though the ideal frequency of such visits has not yet been established. In particular, the lack of diagnostic criteria and valid predictors of disease evolution significantly limit patient evaluation and the use of potentially effective drugs in the earliest phase of the disease.

At present, no drug or combination of drugs has been studied adequately at the very early stages of the disease, which challenges the usefulness of early diagnosis. Nevertheless, the survival of patients with SSc has improved in the past 25 years following the introduction of calcium channel blockers, angiotensin-converting enzyme inhibitors, cyclophosphamide, methotrexate and endothelin receptor antagonists/phosphodiesterase inhibitors/prostanoids. These drugs, recommended in SSc [22] as well as other treatments being used in therapeutic trials, make it necessary to attempt to define SSc at a stage when treatment may be more effective and may induce durable remission.

Early diagnosis of disease complications

In SSc severe organ-based complications are frequently observed: interstitial lung disease (ILD), digital ulceration (DU), SSc renal crisis, sudden death and pulmonary arterial hypertension (PAH). These complications produce the high case-specific mortality rate observed among patients with SSc [5,23]. Data show that over two-thirds of deaths between 1990 and 2002 were caused by internal organ complications, and that pulmonary complications carry the worst prognosis [6]. The main question is: 'is there a possibility of early diagnosis in order to prevent these complications?'

Digital ulcers

The most common manifestation of vascular abnormalities in SSc is RP. Blood vessels abnormally react to stimuli, vasoconstricting

continuously and thus leading to digital ischemia and the development of long-term complications such as digital ulcers and necrosis (FIGURE 1) [24].

In patients with limited SSc, DUs represent one of the most frequent manifestations of microangiopathy. They cause pain, especially when infected, limit hand function, digital resorption and osteomyelitis, and often require hospital-based treatments. DU affects approximately half of patients with SSc, and an estimated 75% of affected patients experience their first episode within 5 years of their first non-RP symptom [25].

The early detection of patients with a high risk of developing DU could allow a preventive treatment, with a reduction of morbidity and social costs.

Nailfold videocapillaroscopy (NVC) is an imaging technique for microcirculation study and it represents one of the most reliable tools for the classification and diagnosis of SSc and related conditions [26,27]. Although the diagnostic value of NVC in the differentiation between primary and secondary RP is sufficiently defined [26,27], the usefulness of NVC in the follow-up of patients with SSc remains uncertain, namely in its correlation with disease activity/severity and its predictive role in SSc complications (FIGURE 3) [28–30].

Sebastiani *et al.* have developed a capillaroscopic skin ulcer risk index that can predict the onset of new digital ulcers by using NVC in patients with SSc. This index considers the total number of capillaries in the distal row (N), maximum loop diameter (D), number of megacapillaries (M) and the M:N ratio [31]. Alivernini *et al.* reported that the best independent DU predictors in SSc patients are IL-6 levels higher than 2 pg/ml, lupus anticoagulant positivity and the presence of avascular areas on nailfold videocapillaroscopic analysis [32]. In their SSc cohort, skin ulcers were present simultaneously with other vascular comorbidities, such as the reduction of transfer coefficient for carbon monoxide, the presence of PAH, a higher interstitial lung score, a history of arrhythmias and the presence of heart block signs, which suggests that these lesions could be part of a systemic process mainly characterized by endothelial damage. These results could be useful for the physician in daily practice to identify which SSc patients have a higher risk of developing skin ulcers during the course of the disease. This diffuse SSc subset, with lung and cardiopulmonary involvement, thrombophilia and avascular areas on NVC, represent the major risk factors for DU development [32].

In conclusion, follow-up with NVC (every 6 months) is suggested for all RP patients.

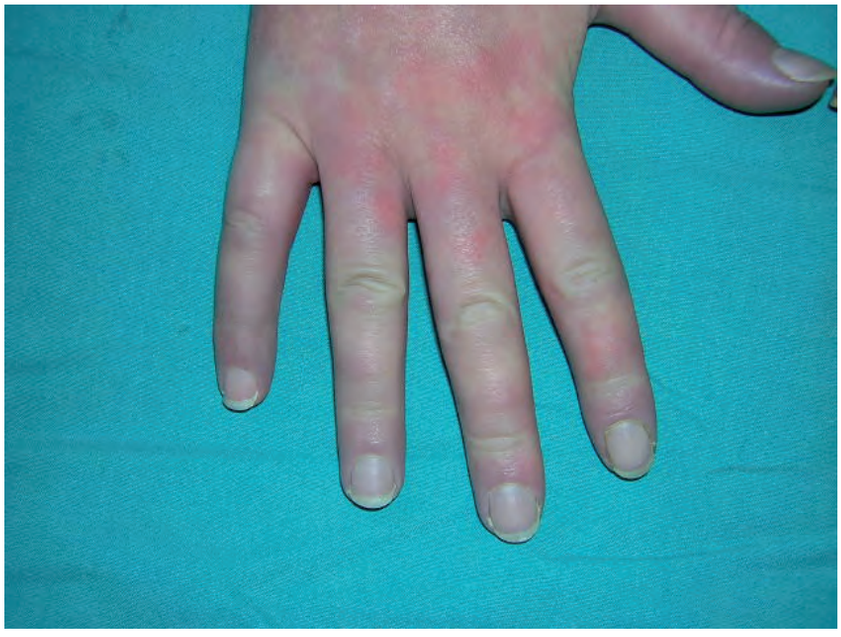

Figure 2. Puffy fingers in a patient characterized by active Raynaud's phenomenon, antinuclear antibodies, and topoisomerase I positive and capillaroscopy pattern. The patient will develop a very aggressive diffuse systemic sclerosis after a few months.

Sudden cardiac death

Scleroderma may affect virtually all cardiac structures and is associated with an increased risk of death [33]. Symptoms such as palpitations or syncope are predictive of ECG abnormalities in patients with SSc [34]. Clinical factors such as age and systemic extent of disease appear to correlate with cardiac rhythm disturbances observed by ambulatory electrocardiography, although conflicting data exist regarding the predictive value of lung disease on the incidence of ventricular tachyarrhythmias. Interestingly, sex, duration of disease, extent of skin involvement and presence of serum anticentromere antibody do not

Box 1. Preliminary criteria, still to be validated, for the very early diagnosis of systemic sclerosis†.

- Major criteria
  - Raynaud's phenomenon
  - Antibodies (antinuclear, anticentromere, anti-topoisomerase I)
  - Diagnostic nailfold videocapillaroscopy
- Additional criteria
  - Calcinosis
  - Puffy fingers
  - Digital ulcers
  - Dysfunction of the esophageal sphincter
  - Telangiectasia
  - Ground glass at chest high-resolution computed tomography

†*Provisional criteria for the diagnosis of very early systemic sclerosis proposed by EULAR Scleroderma Trial and Research group (EUSTAR) (to be validated through a Delphi Technique). Diagnosis will be achieved when at least three major criteria are satisfied or two major plus one additional criteria are satisfied.*
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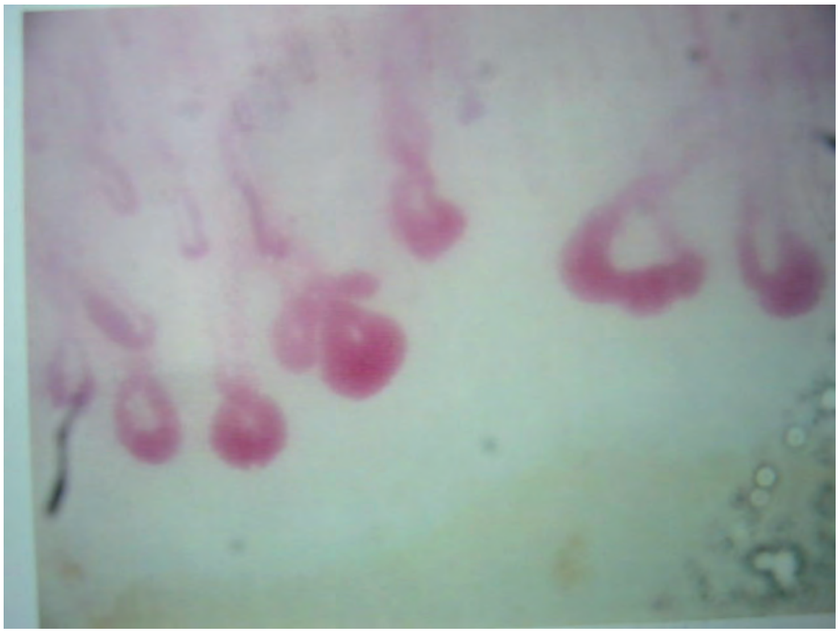

Figure 3. Nailfold videocapillaroscopy: megacapillaries in a patient with early typical scleroderma capillaroscopic pattern. The patient will develop lung involvement 7 years later.

appear to predict ventricular arrhythmias [35]. Ambulatory electrocardiography is also useful for the risk stratification of patients with scleroderma. Ventricular ectopy and tachyarrhythmias found on ambulatory monitoring are associated with increased mortality.

Kostis *et al.* reported that ventricular tachycardia was associated with a twofold increase in the risk of death, whereas frequent ventricular ectopy, defined as more than 100 premature ventricular contractions per 24 h, was associated with a fourfold increase in the risk of death, and ectopy, defined as more than 1000 premature ventricular contractions per 24 h, was associated with a sixfold increased risk of death [35]. Other risk factors of developing tachyarrhythmias are a prolonged QTc interval, heart rate variability and PR interval prolongation.

The presence of cardiac involvement in SSc is often underestimated due to the occult nature of the signs and symptoms, and reports of the prevalence of cardiac disease vary depending on the methods used. Moreover, symptoms of cardiac manifestations are often attributed to noncardiac causes such as pulmonary, musculoskeletal or esophageal involvement. More recent studies suggest that clinical evidence of myocardial disease may be seen in 20–25% of patients with SSc [36]. Autopsy studies have observed myocardial fibrosis and pericardial disease to be most prevalent, but like any autopsy study, this likely represents patients with more advanced disease [37–39]. With thallium scintigraphy the estimated prevalence of clinical cardiac involvement in SSc is much higher [40–44]. Other modalities such as single photon emission computed tomography thallium imaging have been noted in nearly all SSc patients tested [42–44], but the clinical implications of these defects remain uncertain. In addition to thallium and MRI studies, echocardiography has been used to screen SSc patients for asymptomatic cardiac abnormalities. In a study of 54 patients, 69% were found to have an abnormality by echocardiogram [45], the most common abnormalities were elevated right ventricular systolic pressure, pericardial effusion, increased right ventricular dimension and left atrial enlargement. In addition to structural defects, 24 h ambulatory monitoring has detected arrhythmias and conduction system abnormalities in SSc patients with or without symptoms [46,47]. MRI is a reliable and sensitive technique to diagnose heart involvement in SSc and to analyze its mechanisms, including its inflammatory, microvascular and fibrotic components. Compared with echocardiography, MRI appears to provide additional information by visualizing myocardial fibrosis and inflammation [48].

Cardiac MRI can provide information regarding myocardial perfusion. In the 'ischemic cascade' of ischemic heart disease, hypoperfusion will lead first to diastolic and then to systolic ventricular dysfunction. We considered that cardiac MRI would have the potential to make a diagnosis of cardiac involvement in SSc earlier than echocardiography, since it enables dynamic first-pass perfusion MRI of the entire left-ventricular myocardium, with improved imaging quality and higher spatial resolution [49].

As it is noninvasive, quantitative and highly sensitive, MRI appears as a method of choice to determine the natural history of untreated patients or to accurately monitor the effects of treatment. It has been reported that MRI gives a higher sensitivity than echocardiography even if echocardiography is more useful in valvular heart diseases, especially in PAH screening with tricuspid gradient evaluation [48].

The tool identifying patients at risk of malignant arrhythmias still remains Holter ECG. This tool allows the detection and monitoring of critical arrhythmias in order to prevent sudden death with cardioverter defibrillator implantation [50]. All SSc patients should be monitored routinely by ambulatory electrocardiography, echocardiography and Holter ECG and, if necessary, further examinations should be performed (MRI, single photon emission computed tomography).

ILD & pulmonary hypertension

Pulmonary complications are among the most common and deadly manifestations of SSc and most often comprise fibrosis or ILD and pulmonary vascular disease leading to PAH [51].

Dyspnea on exertion, hypoxemia and nonproductive cough are the most common manifestations of pulmonary fibrosis, even in patients without radiological evidence of pulmonary damage. Hemoptysis can also be observed in advanced fibrosis. Fine bibasilar crackles at chest auscultation are characteristic.

Abnormalities of pulmonary function tests (PFTs) are common in patients with SSc, although for many patients these are relatively minor. Using PFTs, significant pulmonary involvement is detectable in 25% of the patients with SSc within 3 years of diagnosis. Differentiation between ILD, PAH and other causes of dyspnea in patients with SSc can be clinically difficult. However, the identification and staging of pulmonary manifestations is of paramount importance for the management of patients [52]. In fact, early diagnosis of ILD is required because the disease is progressive and treatment in the later stages, when advanced fibrosis is present, gives scarce results. Chest high-resolution computed tomography is recognized as a sensitive tool for predicting the histological characteristic of the lung parenchymal abnormalities. Pathological findings show that nonspecific interstitial pneumonia is the principal pattern in SSc, while interstitial pneumonia is usually more rare. In SSc-ILD, there is prominent ground-glass opacification in well over half of patients. Ground glass can predominate, but more often overlaps with an equally extensive reticular pattern. However, the problem for the clinician is that ground glass on CT is not synonymous with inflammation (alveolitis), as we do not know if it represents edema or already fine fibrosis. Ground glass is more likely to be due to fibrosis when admixed with reticular abnormalities and especially when traction bronchiectasis is present. However, even when reticular abnormalities and traction bronchiectasis are both apparent, a component of inflammation cannot be excluded [53].

It has been reported that the risk factors for severe pulmonary fibrosis are early, diffuse scleroderma with an anti-topoisomerase antibody or a nucleolar pattern on ANA. Patients who already have a decreased forced vital capacity in the first 12–18 months are at the highest risk. Patients with serial PFTs that decrease by more than 10% are also at increased risk. A reduction in diffusion lung capacity for carbon monoxide (DLCO) is reportedly an early sign of pulmonary disease in SSc, as well as an important predictor of mortality [54]. Based on the observations of Steen [55], the risk of progression of SSc-ILD is highest in the first 4 years of systemic disease, and especially in the first 2 years and in a small subset of patients in whom lung disease precedes the cutaneous manifestations of SSc. Regular monitoring of PFTs is especially important during the first 4 years. In conclusion, high-resolution computed tomography (ground glass) and PFTs (reduction of DLCO and forced vital capacity) are the gold standard for early detection and prediction of lung fibrosis and its evolution in SSc patients.

The treatment of ILD is based on immunosuppressant agents, but the results are often disappointing, especially in advanced SSc. There is no proven treatment to prevent disease progression.

Although cyclophosphamide demonstrated efficacy in ILD in SSc [56,57], its prolonged administration has been associated with long-term complications such as an increased rate of malignant disease [58]. The use of azathioprine, following intravenous pulse cyclophosphamide, has been associated with stable or improved PFT in 70 and 51.8% of SSc patients at 6 months and 2 years, respectively [59].

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure of 25 mmHg at rest with a normal pulmonary capillary wedge pressure (<15 mmHg) [60]. Microvascular lesions underlie many manifestations of SSc, including PAH, which results from diffuse noninflammatory occlusive lesions of the precapillary arterioles in the lung.

Pulmonary arterial hypertension is one of the most severe complications of SSc and it is related to very high mortality. It develops in approximately 9% of SSc patients with a survival of 30–50% at 3 years and is associated with a limited subset of disease [61]. Early detection of PAH is challenging because its symptoms (dyspnea, fatigue and exercise intolerance) are nonspecific and overlap with those of other morbidities of SSc, including pulmonary fibrosis and cardiomyopathy. Once established, severe PAH is difficult to treat and has a poor prognosis [62,63]. Currently, identification of PAH often occurs late in the course of SSc, with up to 81% of the patients categorized as New York Heart Association (NYHA) class III or IV at the time of PAH diagnosis [64]. Identification of risk factors or predictors of the development of PAH in individuals with SSc would allow earlier diagnosis and initiation of specific therapy for PAH at a time when it is most likely to be effective [65]. Allanore *et al.* reported that elevated

levels of NT-proBNP predict the occurrence of PAH [66]. BNPs (BNP and NT-proBNP) have emerged in recent years as important diagnostic and prognostic markers of cardiac failure. Studies in patients with PAH have demonstrated that plasma BNP levels are increased in proportion to the extent of right ventricular dysfunction [67,68]. There is growing evidence that the BNP level might be a biomarker for PAH in terms of screening, diagnostic evaluation, evaluation of response to therapy and prediction of disease severity [69]. They also suggest that it is possible to identify 'pre-PAH' or 'early PAH' using accurate measures of the DLCO:alveolar volume (VA) ratio as a reflection of capillary gas exchange and NT-proBNP levels as a reflection of cardiac wall stress. Moreover, the combination of these two variables is a very strong predictor of the development of PAH. They recommend that SSc patients with both a DLCO of 70% or less and elevated NT-proBNP levels should be very carefully monitored, and they suggest that such patients would constitute an appropriate target group for investigation of early therapeutic intervention for PAH in a randomized trial. Hofstee *et al.* reported that a reduction in nailfold capillary density, but not capillary loop dimensions, is associated with PAH, and correlates with the severity of PAH in both SSc and idiopathic PAH. This suggests that either systemic microvascular changes play a part in the development of PAH, or that PAH itself contributes to systemic microvascular changes [70]. ECG, chest x-ray, PFTs and serological markers can provide findings suggestive of or supporting the diagnosis of PAH, but only an echocardiography is recommended as a screening tool for detection of PAH [71], and regular echocardiographic examination is mandatory in all SSc patients, even in the absence of any symptoms. In cases of abnormal values of pulmonary arterial pressure on an echocardiography, catheterization in the right side of the heart is required to confirm the diagnosis of PAH, and to test the vasoreactivity of the pulmonary circulation [71]. Besides calcium channel blockers in the vasoreactive responders, the treatment of PAH is based on intravenous, inhaled and oral prostanoids (iloprost, epoprostenol, treprostinil and beraprost), endothelin receptor antagonists (bosentan, sintaxentan and ambrisentan) and phosphodiesterase type-5 inhibitors (sildenafil and tadalafil). Epoprostenol is the only treatment shown to improve survival in PAH [72]; bosentan increases time to clinical worsening [73], while the others only demonstrated efficacy in improving exercise capacity, symptoms and hemodynamics [74–76].

In conclusion, the DLCO:VA ratio, NT-proBNP levels and nailfold capillaroscopy can be used to identify SSc patients who are at high risk for the development of PAH. This has important clinical implications as noninvasive tests (laboratory tests, PFTs and echocardiography) may be used to identify high-risk patients who should undergo right heart catheterization.

Renal crisis

Despite the use of angiotensin-converting enzyme inhibitors to prevent scleroderma renal crisis (SRC), it occurs in 6% of all patients with SSc, and in 10–15% of those with diffuse SSc; 40% of the patients may require dialysis, and mortality at 5 years is 30–40%.

The course of SRC is characterized by an abrupt onset of hypertension, acute renal failure, headaches, fevers, malaise, hypertensive retinopathy, encephalopathy and pulmonary edema. It is difficult to make an early diagnosis of SRC at the very early stages of onset; usually patients come late to the observation of the tertiary center. These patients must be educated to inform the center directly if any of the most important signs of symptoms occur. Early diagnosis and treatment may, thus, be crucial in improving outcomes.

Patients at greatest risk of developing SRC are those with diffuse cutaneous or rapidly progressive forms of SSc, a recent onset of SSc without evidence of RP, recent initiation of corticosteroid therapy, even at low doses, the presence of tendon friction rubs, pericardial effusion, large joint contractures, anemia, cardiac insufficiency and new cardiac events.

Laboratory tests may demonstrate hypercreatinemia, microangiopathic hemolytic anemia, thrombocytopenia and hyperreninemia.

Renal crisis is also linked to a positive ANA speckled pattern, antibodies to RNA polymerase I and III and an absence of anticentromere antibodies [77]. Recently, it has been reported that changes in anti-RNA polymerase antibody levels may also reflect changes in skin score, and disappearance of these antibodies during follow-up predicts milder disease and better survival [78].

In conclusion, in SSc patients, renal function has to be regularly monitored by laboratory tests, creatinine clearance and renal echo doppler in order to exclude the presence of an increased renal resistance index.

Gastrointestinal involvement

Involvement of the GI tract occurs in almost all patients with SSc and is associated with a poor QOL, a more severe prognosis and a reduced

survival. All the parts of the GI tract may be involved, and the esophagus is affected in 70–90% of SSc patients [79]. Impaired peristaltic contractions of the distal two-thirds of the esophagus and decreased lower esophageal sphincter pressure characterize initial esophageal involvement, and may be followed in later phases by uncoordinated esophageal motility or complete esophageal paralysis with atonia of lower esophageal sphincter [80]. These alterations cause gastroesophageal reflux and subsequent esophagitis that may lead, if not treated, to erosions, bleeding, stricture formation, fistulae and an achalasia-like syndrome. Extraesophageal manifestations of gastroesophageal reflux as pharyngitis, mouth ulcers, chronic cough, asthma and recurrent pneumonia may also occur. Esophageal x-ray with barium, esophageal manometry, endoscopy and 24-h pH monitoring are currently used for diagnosis of esophageal involvement and its complications. Gastric antral vascular ectasia or 'watermelon stomach' is another complication of SSc consisting on a endoscopic image of ectasic blood vessels that radiate from the antrum to the pylorus as parallel red lines similar to the stripes on a watermelon. Gastric antral vascular ectasia may manifest as occult gastric bleeding, and it may be associated with atrophic gastritis, achlorhydria and B12 deficiency. Small bowel involvement is characterized by impaired motility leading to luminal dilatation, formation of diverticuli and pseudoobstruction, which may be complicated by bacterial overgrowth, bleeding and perforation [80]. Malabsorption and incorrect alimentation related to microstomy and gastro–esophageal involvement are responsible for malnutrition. The colon may also be affected with delayed intestinal transit and constipation in patients in whom diarrhea and malabsorption have not yet occurred. It may be complicated by colonic telangiectasia and pseudodiverticula, leading to bleeding and obstruction. The involvement of the anal sphincter together with rectum collagen deposition may lead to fecal incontinence that is reported in up to 38% of SSc patients [81].

Table 1. Main instrumental and laboratory investigations, signs and symptoms for early diagnosis in systemic sclerosis.

Early diagnosis	Instrumental and laboratory investigations, signs and symptoms
SSc	RP, puffy fingers, ANA (anticentromere antibodies and anti-topoisomerase I) and capillaroscopy
PAH	Echocardiography, PFTs, NT-proBNP and right heart catheterization
ILD	PFTs and chest HRCT

ANA: Antinuclear antibodies; HRCT: High-resolution computed tomography; ILD: Interstitial lung disease; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAH: Pulmonary arterial hypertension; PFT: Pulmonary function test; RP: Raynaud's phenomenon; SSc: Systemic sclerosis.

Conclusion & future perspective

Currently, the early diagnosis of SSc and related organ involvement is possible (Tables 1 & 2). In fact, RP, ANA and puffy fingers, identified as red flags, and specific antibodies (anticentromere antibodies and anti-topoisomerase I) and capillaroscopy may be of great help in identifying very early SSc patients at risk of progression to overt disease.

In the future, we might also have a 'window of opportunity' in very early SSc where the disease may be stopped before skin and internal organs are irreversibly damaged [82]. This perspective is now challenging the whole community [20], as predictive criteria remain to be developed and a targeted therapy still needs to be identified. To this task only prospective studies can lead to the validation of these new criteria and research may definitively help to find the best therapy, which might contribute to preventing the pathogenetic cascade of SSc.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 2. Predictors, progression and outcome complications in systemic sclerosis.

Prediction	Signs/symptoms	Progression	Outcome
SRC	dSSc, tendon friction rubs, steroids and anti-RNA polymerase III	Renal insufficiency, malignant hypertension	Death
Digital ulcers	Rapidly progressing skin involvement, digital pitting scars, calcinosis high levels of IL-6, LAC and avascular areas at NVC	Gangrene, osteomyelitis, septicemia	Amputation, death
Heart involvement (only electrical)	Ventricular ectopy and tachyarrhythmias, QTc interval, heart rate variability and PR interval prolongation		Sudden death

dSSc: Diffuse systemic sclerosis; LAC: Lupus anticoagulant; NVC: Nailfold videocapillaroscopy; SRC: Scleroderma renal crisis.

Executive summary

Predicting risk factors for digital ulcers

- Diffuse systemic sclerosis (SSc) subset, lung and cardiopulmonary involvement, thrombophilia and avascular areas on nailfold videocapillaroscopy, represent the major risk factors for digital ulceration development. Digital pitting scars, calcinosis, IL-6 levels higher than 2 pg/ml and lupus anticoagulant positivity are also risk factors.

Predicting risk factors for sudden cardiac death

- Palpitations or syncope, age and systemic extent of disease appear to correlate with cardiac rhythm disturbances observed by ambulatory electrocardiography. Ventricular ectopy and tachyarrhythmias are associated with increased mortality. Other risk factors of developing tachyarrhythmias are a prolonged QTc interval, heart rate variability and PR interval prolongation.
- This can be monitored by routinary ambulatory electrocardiography, echocardiography and Holter ECG and, if necessary, by performing further examinations (MRI and single photon emission computed tomography).

Predicting risk factors for pulmonary arterial hypertension

- Elevated levels of N-terminal pro-B-type natriuretic peptide and reduction of the diffusing capacity of carbon monoxide per liter of alveolar volume are risk factors. Furthermore, a reduction in nailfold capillary density, but not capillary loop dimensions, is associated with pulmonary arterial hypertension (PAH), and correlates with the severity of PAH in both SSc and idiopathic PAH.
- Laboratory tests, pulmonary function tests, echocardiography and, eventually, right cardiac catheterization are recommended.

Predicting risk factors for renal crisis

- Diffuse cutaneous or rapidly progressive forms of SSc, a recent onset of SSc without evidence of Raynaud's phenomenon, the recent commencement of treatment with a corticosteroid, and the presence of tendon friction rubs, positive antinuclear antibodies speckled pattern, antibodies to RNA polymerase I and III, and an absence of anticentromere antibodies are risk factors for renal problems.
- Renal function has to be regularly controlled by laboratory test, creatinine clearance and echo Doppler renal artery.

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▪▪ **Difficulties inherent in diagnosing, screening and treating systemic sclerosis are reported and early diagnosis has been recommended.**

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