Seminars in Arthritis and Rheumatism 51 (2021) 969–976

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Incidence, prevalence and long-term progression of Goh algorithm rated interstitial lung disease in systemic sclerosis in two independent cohorts in flanders: A retrospective cohort study

Els Vandecasteele[1,2,a], Karin Melsens[1,3,a], Amber Vanhaecke[1,3,a], Daniel Blockmans[4], Carolien Bonroy[5,6], Charlotte Carton[1], Ellen Deschepper[7], Filip De Keyser[1,8], Frédéric Houssiau[9], Yves Piette[1,3], Marie Vanthuyne[9], Koen Verbeke[1,10], Rene Westhovens[11,12], Wim A. Wuyts[13], Ellen De Langhe[11,14], Guy Brusselle[1,10,15], Vanessa Smith[1,3,16,*]

[1] Department of Internal Medicine, Ghent University, Ghent, Belgium
[2] Department of Cardiology, Ghent University Hospital, Ghent, Belgium
[3] Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
[4] Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium
[5] Department of Diagnostic Sciences, Ghent University, Ghent, Belgium
[6] Department of Laboratory Medicine, Ghent University Hospital, Ghent, Belgium
[7] Biostatistics Unit, Department of Public Health and Primary Care, Ghent University, Ghent, Belgium
[8] Department of Rheumatology, Ghent University Hospital, Ghent, Belgium and praktijk10A, Maldegem, Belgium
[9] Department of Rheumatology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Louvain-la-Neuve, Belgium
[10] Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[11] Division of Rheumatology, University Hospitals Leuven, Leuven, Belgium
[12] Skeletal Biology and Engineering Research Centre, Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[13] Department of Respiratory Medicine, Unit for interstitial lung diseases, University Hospitals Leuven, Leuven, Belgium
[14] Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium
[15] Departments of Epidemiology and Respiratory Medicine, ErasmusMC, Rotterdam, the Netherlands
[16] Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Center (IRC), Ghent, Belgium

ARTICLE INFO

Keywords:
Systemic sclerosis
Early systemic sclerosis
Interstitial lung disease
Epidemiology
Prevalence
Incidence and progression

ABSTRACT

Objectives: The epidemiology of interstitial lung disease (ILD) in systemic sclerosis (SSc) in Belgium is unknown. In literature, its prevalence varies between 19% and 52% in limited/diffuse cutaneous SSc (LcSSc/DcSSc). However, its prevalence in "early" SSc (pre-clinically overt SSc without [yet] skin involvement), nor its incidence rate in SSc (LcSSc/DcSSc/"early" SSc) has ever been described. Against this background, we aimed to determine the prevalence/incidence (rate) and progression of ILD in SSc.

Methods: 12-year follow-up data of consecutive SSc patients, included in two Flemish cohorts (University Hospitals Ghent and Leuven), were retrospectively analysed. ILD was classified according to the simplified Goh algorithm. Progression of ILD was defined as a relative decline of FVC ≥10%, a combined relative decline of FVC 5-10% and DLCO ≥15%, or as an increase in HRCT extent.

Results: 722 patients (60% LcSSc/ 20% DcSSc/ 20% "early" SSc, median (IQR) follow-up 39 [12-80] months) had baseline HRCT. 243 were rated to have ILD at baseline and 39 during follow-up (prevalence of 34%/ incidence rate of 20.3/1000PY, 95%CI:14.5-27.8). Amongst those with baseline ILD, 60% had lung functional progression at five years of follow-up. In the "early" SSc subgroup, eight patients were rated to have ILD at baseline and three during follow-up (prevalence of 6%/ incidence rate of 5.8/1000 PY, 95%CI:1.2-17.0).

* Corresponding author.
E-mail addresses: els.vandecasteele@ugent.be (E. Vandecasteele), karin.melsens@ugent.be (K. Melsens), amber.vanhaecke@ugent.be (A. Vanhaecke), daniel.blockmans@uzleuven.be (D. Blockmans), carolien.bonroy@uzgent.be (C. Bonroy), charlotte.carton@ugent.be (C. Carton), ellen.deschepper@ugent.be (E. Deschepper), filip.dekeyser@praktijk10a.be (F. De Keyser), frederic.houssiau@uclouvain.be (F. Houssiau), yves.piette@azsintjan.be (Y. Piette), marie.vanthuyne@uclouvain.be (M. Vanthuyne), koenverbeke100@gmail.com (K. Verbeke), rene.westhovens@uzleuven.be (R. Westhovens), wim.wuyts@uzleuven.be (W.A. Wuyts), ellen.delanghe@uzleuven.be (E. De Langhe), guy.brusselle@uzgent.be (G. Brusselle), vanessa.smith@ugent.be (V. Smith).
[a] Els Vandecasteele, Karin Melsens and Amber Vanhaecke are shared first authors.

https://doi.org/10.1016/j.semarthrit.2021.07.018

Conclusion: Both LcSSc and DcSSc patients should be monitored for ILD evolution. The low prevalence and incidence of ILD in the “early” SSc subgroup may instruct future decisions on the construction of uniform patient follow-up pathways in “early” SSc.

Introduction

Systemic Sclerosis (SSc) is an orphan auto-immune connective tissue disease (CTD) characterised by vasculopathy, auto-immunity and fibrosis of skin and visceral organs [1]. Progressive fibrosis of skin and internal organs results in major organ damage and high morbidity and mortality [2-5]. Nowadays, pulmonary complications (interstitial lung disease [ILD] and pulmonary arterial hypertension [PAH]) are the leading causes of SSc-related mortality, counting for up to 60% of the disease related mortality in clinically overt SSc (more specifically, limited cutaneous SSc [LcSSc] and diffuse cutaneous SSc [DcSSc]) [2,3].

In literature, the prevalence of ILD in SSc ranges between 19% and 52% [6]. The incidence rate of ILD in SSc remains unknown. Nihtyanova et al. described a cumulative incidence of clinically significant ILD of 34% and 16% in the DcSSc and LcSSc subgroups at five years follow-up [7]. Most patients develop restrictive lung disease in the first five years and ILD might even be the first clinical presentation [7-10]. It is also known that the extent of lung fibrosis correlates with mortality in SSc [11, 12]. However, nowhere in literature, data are available concerning the prevalence and incidence in an “early” SSc cohort, which is prone to develop clinically overt SSc, more specifically in a cohort of patients with Raynaud’s phenomenon and a specific SSc-antibody and/or an SSc pattern on nailfold capillaroscopy but without (yet) skin involvement [13-16].

Until recently, there was no consensus on how ILD in SSc should be diagnosed, and how SSc patients should be screened for ILD progression, resulting in discrepancies in the assessment and reported frequency of occurrence and progressiveness of ILD in SSc [6,17]. In 2018, a survey showed that only half of the general rheumatologists and two-thirds of the SSc experts routinely obtain a high-resolution computerised tomography (HRCT) in newly diagnosed SSc patients [18]. Recently, SSc experts agreed that HRCT is the gold standard for diagnosing ILD [12,19,20]. In 2008, Goh et al. proposed an easily applicable algorithm for staging ILD in SSc patients as limited or extensive ILD based on the identification of disease extent on HRCT, combined with a forced vital capacity (FVC) estimation in cases with indeterminate disease extent on HRCT [11].

Once ILD has been diagnosed, it is important to organise strict follow-up since ILD has a variable clinical course. Most patients will experience a slow decline in lung function, but some will progress rapidly after disease onset [21-23].

An optimal definition of "progressive ILD" was recently proposed by the Outcome Measures in Rheumatology (OMERACT) CTD-ILD Working Group, based on FVC and diffusion capacity of the lung for carbon monoxide (DLCO) decline. ILD progression is defined as either a relative FVC decline from baseline of $\geq$10% or a relative FVC decline of 5-10% combined with a relative DLCO decline of $\geq$15% [24]. Goh et al. found that this definition for ILD progression in SSc was independently predictive of mortality at 1 and 2 year of follow-up [25]. Additionally, an increase in the radiographic extent of ILD on HRCT would also signify progression [26].

Against this background, we aim to determine the prevalence and incidence rate of ILD (according to the simplified flow diagram described by Goh et al.) in our 12-year multicentre standardised SSc cohort, and for the first time in a subgroup of “early” SSc patients [11,19,20,26-28].

Methods

Patient selection

Up to 12-year follow-up data of consecutive adult SSc patients were obtained from two Flemish expert centres on SSc (Ghent University Scleroderma Unit and University Hospitals Leuven SSc cohort). The patients in the cohort consist of patients from academic and community centres, being referred to the tertiary University centres in Ghent and Louvain. Data from each SSc-specific visit between May 2006 and December 2018, collected according to the national Belgian SSc cohort, were evaluated [29]. All patients fulfilled the 2001 LeRoy and Medsger criteria for “early” SSc and/or the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc [13,14,30].

Patients were classified as LcSSc, DcSSc, or “early” SSc without skin involvement, according to the LeRoy classification criteria [13, 14]. Patients with a definite overlap diagnosis with another connective tissue disease or a disease in which ILD might occur, were excluded from analysis. Approval was obtained by the Ethics Committee of the Ghent University Hospital (EC/2008/385) and by the University Hospitals Leuven (S52057). All patients signed informed consent prior to inclusion in this prospective registry.

Systemic sclerosis specific visit

As previously described, a SSc specific visit includes the recording of a patient’s medical history and drug intake and a standard clinical examination with the measurement of skin involvement (modified Rodnan Skin Score [mRSS]) [29,31]. A transthoracic echocardiography, a pulmonary function test (PFT, including FVC and DLCO, expressed as % of the predicted value [% pred]), a standard blood test and an electrocardiography were done at each visit [20,29,32]. An HRCT scan was performed at baseline. Optional investigations (HRCT on visits besides the baseline visit, six minute walk test, right heart catheterisation, ventilation-perfusion scintigraphy and arterial blood gas sampling) were obtained according to clinical practice guidelines [20,33].

Interstitial lung disease

Patients were classified into three subgroups (“no ILD”, limited ILD or extensive ILD), according to the simplified flow diagram described by Goh et al [11]. Each HRCT was centrally analysed and interpreted for the sake of this study in 2019 in the Ghent University Hospital, by an experienced investigator (EV) who was blinded to the patient data [34,35]. Patients were classified in the “no ILD” subgroup when no disease specific abnormalities (reticulations or ground-glass opacities) were detected on HRCT. Limited ILD was defined as extent of disease on HRCT $<$20% or FVC $\geq$70% pred when the disease extent on HRCT was indeterminate [11]. Extensive ILD was defined as extent of disease on HRCT $>$20% or FVC $<$70% pred when the disease extent on HRCT was indeterminate. Baseline ILD classification was defined at the time of inclusion or when unavailable, as the first ILD classification within the first year of inclusion in the cohort (i.e. at 6-month visit) [34]. During the follow-up visits, patients kept their former classification, or were re-evaluated with HRCT when the clinical

examination or PFT changed at the discretion of the local multidisciplinary teams [34,35].

ILD progression during follow-up visits was determined based on both lung functional parameters and HRCT, in the subgroup of patients with Goh algorithm rated limited or extensive ILD at baseline [11]. The definition of the OMERACT CTD-ILD Working Group was used to define lung functional progression during follow-up visits compared to baseline values (a relative FVC decline ≥10% or a combined relative FVC decline of 5-10% with a relative DLCO decline ≥15%) [19,24]. An increase in the radiographic extent of ILD on HRCT, i.e. evolution from baseline limited ILD to extensive ILD according to the Goh algorithm, during follow-up visits, was interpreted as HRCT progression [26]. The progressiveness of baseline ILD was evaluated at 1, 2, 3, 5, 10 and 12 years of follow-up. Of note, patients evolving from baseline Goh algorithm rated "no ILD" to Goh algorithm rated limited or extensive ILD during follow-up were defined as incidental cases.

Statistical analysis

For descriptive purposes, absolute numbers with percentages are shown for nominal categorical variables, medians with interquartile ranges (IQR) for ordinal categorical and skewed continuous variables and means with standard deviation (SD) for symmetric continuous variables.

The baseline prevalence was calculated by dividing the number of SSc patients with ILD at baseline by the total number of SSc patients included in the cohort. The cumulative prevalence was calculated by dividing the total number of SSc patients with ILD by the total number of SSc patients included in the cohort. The incidence was calculated by dividing the number of SSc patients who evolved from "no ILD" to Goh algorithm rated limited or extensive ILD during follow-up (i.e. "incidental cases"), by the number of SSc patients without ILD at baseline. The incidence rate per 1000 person-years (PY) was obtained by dividing the number of incidental ILD cases by the total number of PY accumulated by the cohort (excluding SSc patients with ILD at baseline). The 95% confidence intervals (95%CI) for a single proportion were measured using the Poisson rate confidence interval [36].

The proportion of patients with lung functional progression/HRCT progression is reported in the total cohort, as well for the subgroups of patients with baseline Goh algorithm rated limited and extensive ILD, and for the different SSc clinical subsets (i.e. LcSSc, DcSSc and "early" SSc) [8,13,14]. Proportions were calculated as the number of events divided by the available observations at the follow-up visits. To assess the uncertainty introduced by missing data at the follow-up visits, a sensitivity analysis was performed, reporting the best- and worst-case scenarios. More specific, in the best-case scenario for patients with missing information, it was assumed that no lung functional progression or no evolution to Goh algorithm rated extensive ILD occurred ('non-events'). In the worst-case scenario, all missing observations were considered 'events'. In both scenarios, proportions were calculated with respect to the total number of patients that could have reached the respective yearly SSc-specific follow-up visit in the cohort, excluding patients passed away prior to the follow-up visit and patients who were lost to follow-up at that particular visit. Statistical analysis was performed with SPSS statistical software, version 25.0.

Results

Baseline characteristics

Between May 2006 and December 2018, a total of 898 consecutive SSc patients were included in the SSc cohorts of the University Hospitals Ghent (n=580, 65%) and Louvain (n=318, 35%). All patients (n=898, 100%) fulfilled the LeRoy and Medsger criteria and 702 (78%) the ACR/EULAR classification criteria [13,30].

Baseline PFT was available for 848 (94%) patients, i.e. for 546/580 (94%) of the Ghent SSc patients and for 302/318 (95%) of those from Louvain. A baseline HRCT was performed in 794 (88%) of the 898 included patients, i.e. in 555/580 (96%) of the Ghent SSc patients and in 239/318 (75%) of those from Louvain.

Amongst the 794 patients with available baseline HRCT, 72 were excluded from analysis due to definite overlap: rheumatoid arthritis (n=21), systemic lupus erythematosus (n=15), idiopathic inflammatory myopathy (n=11), Sjogren's syndrome (n=10), mixed connective tissue disease (n=8), systemic vasculitis (n=3), sarcoidosis (n=2), undifferentiated connective tissue disease (n=1) and Crohn's disease (n=1). Hence, a total of 722 SSc patients was finally retained for the analysis of this study. Their baseline demographic and clinical characteristics are reported in Table 1. The mean age at baseline was 54± 14 years, and 75% were female. Four hundred thirty-five (60%) patients were classified at baseline as having LcSSc, 145/722 (20%) as

Table 1
Baseline characteristics of the 722 SSc patients who had baseline HRCT.

	Total (n=722)	LcSSc (n=435)	DcSSc (n=145)	"Early" SSc (n=142)	ACR/EULAR (n=583)
Age (years), mean±SD	54±14	55±14	54±14	49±14	53±14
Gender (♂/♀), n (%)	179(25%) / 543(75%)	101(23%) / 334(77%)	56(39%) / 89(61%)	22(15%) / 120(85%)	157(27%) / 426(73%)
Disease duration (months), median (IQR)	For 558/722 21 (5-69)	For 417/435 23 (4-74)	For 141/145 16 (7-52)	N/A	For 557/583 20 (4-66)
Entire follow-up duration (months), median (IQR)	39 (12-80)	38 (9-81)	44 (19-79)	32 (6-79)	39 (15-81)
SSc pattern on capillaroscopy[§] [15,16]	552/668 (76.5%)	344/401 (79%)	110/132 (76%)	98/135 (73%)	460/546 (79%)
Anti-centromere antibodies[§]	313/721 (43%)	209/434 (48%)	22/145 (15%)	82/142 (58%)	248/583 (42%)
Anti-topoisomerase I antibodies[§]	161/722 (22%)	84/435 (19%)	70/145 (48%)	7/141 (5%)	147/583 (25%)
Anti-RNApolymerase III antibodies[§,°]	23/714 (3%)	13/429 (3%)	10/144 (7%)	0/142 (0%)	22/576 (4%)
FVC (% pred), median (IQR)	For 692/722 107 (92-120)	For 419/435 109 (95-120)	For 137/145 95 (81-109)	For 136/142 114 (102-123)	For 564/583 106 (91-119)
DLCO (% pred), median (IQR)	For 692/722 73 (60-86)	For 420/435 73 (60-86)	For 136/145 64 (51-75)	For 136/142 81 (69-89)	For 561/583 72 (59-85)
Immunosuppressive/Immunomodulatory therapy[§,*]	232/637 (36%)	134/378 (35%)	67/134 (50%)	31/125 (25%)	200/515 (34%)

ACR: American College of Rheumatology; DcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity of the lung for carbon monoxide; EULAR: European League Against Rheumatism; FVC: forced vital capacity; IQR: interquartile range; LcSSc: limited cutaneous systemic sclerosis; N/A: not applicable; SD: standard deviation; SSc: systemic sclerosis.

§ number of true positives/total number of patients with available data (percent).

° Anti-RNApolymerase III antibodies were determined in Ghent by the Systemic Sclerosis (Nucleoli) Profile Euroline (IgG) lineblot assay (Euroimmun, Lübeck, Germany) and in Louvain by Fluoroenzymeimmunoassay (FEIA) (Thermo Fisher, Uppsala, Sweden).

* of the 232 treated with immunosuppressive or immunomodulatory therapy at baseline, 133 received methotrexate, 116 corticosteroids, 31 hydroxychloroquine, 13 mycophenolate mofetil, 10 d-penicillamin, 8 azathioprine, 2 sulfasalazine, 1 cyclophosphamide, 1 anti-TNF-blocker. Of note, 18 SSc patients received rituximab during follow-up, amongst whom 7 with baseline ILD (1 LcSSc and 6 DcSSc), 6 with incidental ILD during follow-up (1 LcSSc and 5 DcSSc) and 5 DcSSc without ILD.

DcSSc and 142/722 (20%) as "early" SSc. The median (IQR) follow-up of these 722 patients was 39 (12-80) months.

At year 1, 14% (90/640); at year 2, 19% (118/604); at year 3, 19% (104/526); at year 5, 22% (95/249); at year 10, 32% (78/245) and at year 12, 23% (36/153) of the 722 patients who had received baseline HRCT were lost to follow-up. No significant differences were observed in the baseline characteristics of the patients who were in follow-up compared to those who lost follow-up.

Prevalence of ILD in the entire cohort

In the 12-year period, 243 patients were Goh algorithm rated as having ILD at baseline and 39 as developing incidental ILD during follow-up, resulting in a baseline prevalence of 34% (243/722) and a cumulative prevalence of 39% (282/722). Amongst the patients with baseline ILD, 207/243 (85%) were classified as limited ILD and 36/243 (15%) as extensive ILD, according to the Goh algorithm (see Table 2).

Subgroup analysis for the 583/722 SSc patients who fulfilled the ACR/EULAR classification criteria showed a baseline ILD prevalence of 38% (219/583) and a cumulative prevalence of 42% (248/583) (see Table 2).

Prevalence of ILD in different subgroups of SSc

Subgroup analysis for the SSc patients with skin involvement (i.e. classified as having either LcSSc or DcSSc, n=580), revealed a baseline ILD prevalence of 41% (235/580) and a cumulative prevalence of 47% (271/580) (see Table 2).

Amongst the 435 included LcSSc patients, 154 were rated as having ILD at baseline and 26 as developing incidental ILD during follow-up, resulting in a baseline prevalence of 35% (154/435) and a cumulative prevalence of 41% (180/435). Amongst the patients with baseline ILD, 134/154 (87%) were classified as limited ILD and 20/154 (13%) as extensive ILD (see Table 2).

Amongst the 145 included DcSSc patients, 81 were rated as having ILD at baseline and 10 as developing incidental ILD during follow-up, resulting in a baseline prevalence of 56% (81/145) and a cumulative prevalence of 63% (91/145). Amongst the patients with baseline ILD, 66/81 (81%) were classified as limited ILD and 15/81 (19%) as extensive ILD (see Table 2).

Eight patients out of the 142 "early" SSc patients were Goh algorithm rated as having ILD at baseline and another three as developing incidental ILD during follow-up, resulting in a baseline prevalence of 6% (8/142) and a cumulative prevalence of 8% (11/142). Amongst the patients with baseline ILD, 7/8 (87.5%) were classified as limited ILD and 1/8 (12.5%) as extensive ILD (see Table 2).

Incidence (rate) of ILD in the entire cohort

A total of 39 incidental Goh algorithm rated ILD cases (8%) were found during follow-up (see Table 2). For the 479 SSc patients without ILD at baseline, there was a total of 22999 months of follow-up, which results in an incidence rate of 20.3/1000 PY, 95%CI:14.5-27.8.

Subgroup analysis for SSc patients who fulfilled the ACR/EULAR classification criteria revealed 29 incidental cases, resulting in an incidence rate of 19.1/1000 PY, 95%CI:12.8-27.4.

Incidence (rate) of ILD in different subgroups of SSc

Twenty-six incidental ILD cases (9%) were found in the LcSSc group during follow-up (see Table 2). There were 13588 months of follow-up for the 281 LcSSc patients without ILD at baseline, resulting in an incidence rate of 23.0/1000 PY, 95%CI:15.0-33.6.

Ten incidental ILD cases (16%) were found in the DcSSc group during follow-up (see Table 2). There were 3220 months of follow-up for the 64 DcSSc patients without ILD at baseline, resulting in an incidence rate of 37.3/1000 PY, 95%CI:17.9-68.5.

Subgroup analysis for the "early" SSc patients versus those with skin involvement (i.e. classified as having either LcSSc or DcSSc), revealed that three (2%) versus 36 (10%) incidental Goh algorithm rated ILD cases were found during follow-up, resulting in an incidence rate of 5.8/1000 PY, 95%CI:1.2-17.0 versus 25.7/1000 PY, 95%CI:18.0-35.6 respectively (see Table 2).

Progressiveness of ILD in the entire cohort

The progressiveness in the entire cohort of patients with ILD at baseline is visualised in Fig. 1 and data on lung functional progression as well as HRCT-graphic progression at each time-point are represented in detail in supplementary file 1.

At baseline, 243 patients were rated as having ILD (207 limited ILD and 36 extensive ILD). Their median follow-up was 43 months (IQR 17-86).

For the evaluation of lung functional progression, PFT data were available for 154 (135 limited ILD and 19 extensive ILD) at 1 year of follow-up and for 86 (78 limited ILD and 8 extensive ILD) at 5 years of follow-up. There was lung functional progression in 19% (29/154) of them at 1 year of follow-up and in the majority of the patients (52/86, 60%), both in the subgroups with limited (46/78, 59%) and extensive (6/8, 75%) ILD at 5 years of follow-up.

For the evaluation of HRCT progression (from Goh algorithm rated limited ILD at baseline to Goh algorithm rated extensive ILD) at 1 and 5 years of follow-up, 55 respectively 24 HRCTs were available. HRCT progression was seen in 2% (1/55) at 1 year and 21% (5/24) at 5 years of follow-up. Sensitivity analysis corroborated these data (see supplementary file 1).

Progressiveness of ILD in different subgroups of SSc

Data concerning the progressiveness of ILD per SSc subgroup, at different years of follow-up, are depicted in supplementary file 1.

At baseline, 154 LcSSc patients were rated as having ILD (134 limited ILD and 20 extensive ILD). Their median follow-up was 43 months (IQR 16-88). For the evaluation of lung functional progression, PFT data were available for 95 patients (86 limited ILD and 9 extensive ILD) at 1 year of follow-up and for 52 patients

Table 2
Overview of the SSc patients rated as having baseline and incidental Goh algorithm rated ILD.

	Total (n=722)	LcSSc (n=435)	DcSSc (n=145)	"Early" SSc (n=142)	ACR/EULAR fulfilment (n=583)
ILD at baseline, n (%)	**243/722 (34%)**	**154/435 (35%)**	**81/145 (56%)**	**8/142 (6%)**	**219/583 (38%)**
Limited ILD, n (%)	207/243 (85%)	134/154 (87%)	66/81 (81%)	7/8 (87.5%)	185/219 (85%)
Extensive ILD, n (%)	36/243 (15%)	20/154 (13%)	15/81 (19%)	1/8 (12.5%)	34/219 (15%)
Incidence of ILD during follow-up[§]	**39/479 (8%)**	**26/281 (9%)**	**10/64 (16%)**	**3/134 (2%)**	**29/364 (8%)**

ACR: American College of Rheumatology; DcSSc: diffuse cutaneous systemic sclerosis; EULAR: European League Against Rheumatism; LcSSc: limited cutaneous systemic sclerosis; SD: standard deviation; SSc: systemic sclerosis.

[§] Incidence = number of incidental cases (i.e. the number of SSc patients that evolved from baseline Goh algorithm rated "no ILD" to Goh algorithm rated limited or extensive ILD during follow-up) divided by the number of patients without Goh algorithm rated baseline ILD.

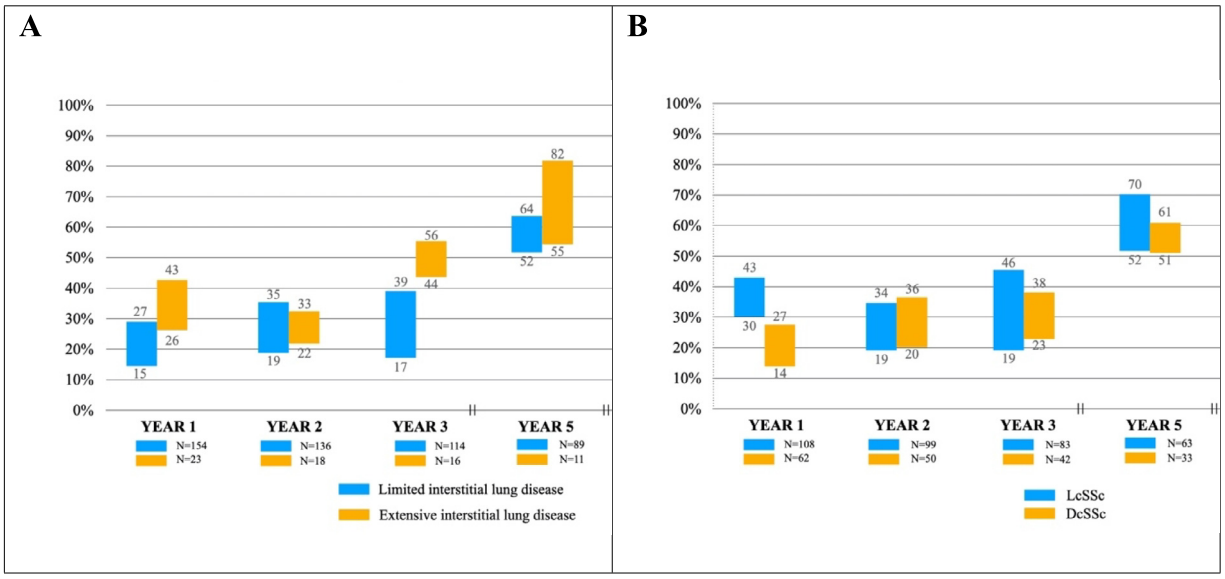

Fig. 1. Estimated ranges of proportions of lung functional progression (best-/worst-case scenario) at annual follow-up versus baseline. DcSSc: diffuse cutaneous systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; Lung functional progression of baseline Goh rated ILD was defined as a relative decline of FVC ≥10% or a relative FVC 5-10% decline combined with a relative DLCO decline ≥15% during follow-up visits compared to baseline. The cohort consisted of a total of 722 SSc patients without overlapping diseases, who had a baseline HRCT. Amongst these 722 SSc patients, 243 were Goh algorithm rated as having ILD at baseline. Figure A represents the estimated ranges of proportions of lung functional progression in the subgroups of patients with limited ILD (blue) versus extensive ILD (orange) at the follow-up visits

(48 limited ILD and 4 extensive ILD) at 5 years of follow-up. There was lung functional progression in 21% (20/95) at 1 year of follow-up and in the majority of them (33/52, 63%) at 5 years of follow-up. At year 5, there was progression in both the subgroups with limited (29/48, 60%) and extensive (4/4, 100%) ILD. For the evaluation of HRCT progression (from Goh algorithm rated limited ILD at baseline to Goh algorithm rated extensive ILD) 29 HRCTs were available at 1 year of follow-up and 15 HRCTs at 5 years of follow up. HRCT progression was seen in 3% (1/29), respectively 27% (4/15).

At baseline, 81 DcSSc patients were rated as having ILD (66 limited ILD and 15 extensive ILD). Their median follow-up was 42 months (IQR 17.5-87). At 1 year of follow-up, PFT data were available for 54 patients (45 limited ILD and 9 extensive ILD) and at 5 years of follow-up, PFT data were available for 30 patients (26 limited ILD and 4 extensive ILD). There was lung functional progression in 18.5% (10/54) at 1 year of follow-up and in the majority of them (17/30, 57%) at 5 years of follow-up. At year 5, there was progression in 58% (15/26) of those having limited ILD at baseline and in 50% (2/4) of those having extensive ILD at baseline. Amongst the 66 DcSSc classified as limited ILD at baseline, an HRCT was performed in 25 patients at year 1 and in 9 of the patients at 5 years of follow-up, showing HRCT progression in 0% (0/25), respectively 11% (1/9).

At baseline, eight “early” SSc patients were rated as having ILD (seven limited ILD and one extensive ILD). Their median follow-up was 43 months (IQR 15-79.5). At 1 year of follow-up, PFT data were available for five patients, showing no progression. At 5 years of follow-up, PFT data were available for four patients with limited ILD at baseline. There was lung functional progression in 50% (2/4) at 5 years of follow-up compared to baseline. No 5-year follow-up PFT data were available for the one patient with extensive ILD at baseline. One patient, with “early” SSc and ILD at baseline, had repeat HRCT at 1 year of follow-up, which showed no progression and no data are available concerning HRCT progression in “early” SSc patients at 5 years of follow-up.

Supportively, the sensitivity analysis performed to cope with the missing data, corroborated all the aforementioned results (Fig. 1 and supplementary file 1).

Discussion

We retrospectively analysed the HRCTs and PFTs in a 12-years Flemish multicentre unselected SSc cohort to determine the epidemiology of ILD in SSc. The main study findings can be summarised as follows: 1) The baseline prevalence of Goh algorithm rated ILD in the entire cohort is 34% and the incidence rate is 20.3/1000PY, 95%CI 14.5-27.8; 2) the small majority of the SSc patients with ILD progresses within 5 years, regardless of their initial classification as limited or extensive ILD and regardless of their clinical subset (LcSSc or DcSSc); and 3) in the “early” SSc group, the baseline prevalence of Goh algorithm rated ILD was low (6%) and only a very small proportion of these “early” SSc patients (2%) developed ILD during follow-up. This low incidence of ILD in the “early” SSc group may be indicative when preparing future guidelines on the follow-up of this particular SSc subset (i.e. those with solely the combination of a Raynaud’s Phenomenon, SSc-specific antibody and/or an SSc pattern on capillaroscopy), as epidemiological data on ILD in this SSc subset are currently non-existent [19,27,37].

The methodological approach using the HRCT-based simplified Goh algorithm allowed us to reliably identify ILD in our unselected SSc cohort. Our baseline ILD prevalence of 34% and cumulative prevalence of 39% are in line with the prevalence reported in different SSc cohorts, ranging between 19% and 52% [6,38,39]. This wide range can, at least partially, be explained by the historical use of different tools to identify ILD in SSc patients (i.e. HRCT and PFT alone or combined), as consensus about the identification of ILD in SSc patients was lacking until recently [18]. As such, we know from literature that HRCT, which has recently been recognised as gold standard for the identification of ILD by the SSc expert community, is not routinely performed in all SSc patients at diagnosis [12,18-20]. For example, in a Dutch SSc cohort, an HRCT was available in less than 50% of the included 654 patients, and in only 80% of patients in a recent Norwegian national SSc cohort [12,39]. In our multicentre study, a baseline HRCT was performed in 88% of the patients, with locoregional differences between the two centres (96% and 75% respectively) (see supplementary files 4 and 5). This study underscores the need to perform a baseline HRCT in all SSc patients. In addition, all patients diagnosed with ILD should be assessed for SSc, not only by evaluating

them for skin involvement and other (clinical) classification criteria, but also for specific SSc-antibodies and/or SSc pattern on nailfold capillaroscopy, before diagnosing them as "idiopathic pulmonary fibrosis" [40].

To our knowledge, the prevalence of ILD in an "early" SSc population, a particular precursor SSc subset, without (yet) skin involvement, has never been described. We found a low baseline ILD prevalence of only 6% and noted that only three of the 134 "early" SSc patients developed Goh rated limited ILD during follow-up (incidence rate of 5.8/1000 PY, 95%CI:1.2-17.0). Importantly, of these "early" SSc patients with incidental ILD, all had Raynaud's phenomenon, SSc specific anti-centromere antibodies and an SSc pattern on nailfold capillaroscopy at baseline [14,41-44]. Consequently, based on these important novel data, we suggest that in an "early" SSc population it may be sufficient to perform an HRCT and lung function test only at baseline, and to monitor these patients during follow-up visits with SSc-specific clinical examination. Our data may suggest, unlike these of the clinically overt forms of SSc (LcSSc and DcSSc) where yearly follow-up is paramount, that the interval between lung functional follow-up periods may be extended over more than one year in "early" SSc.

The progressiveness of ILD was assessed, according to recently consented definitions [24]. We found that the majority of SSc patients with baseline Goh algorithm rated ILD had lung functional progression at 5 years of follow-up (see figure 1) [19,24,45]. Our data are in line with the previous report in 2014 by Nihtyanova et al., describing an increase of the cumulative incidence of clinically significant ILD to 34% in DcSSc patients and 16% in LcSSc patients at 5 years follow-up [7]. Both the Nihtyanova study and our findings corroborate the fact, as stated in recent clinical practice guidelines, that disease monitoring with PFT during follow-up should be rigorous in the clinically overt forms of SSc (DcSSc and LcSSc) [19,20,27].

Finally, our study has the limitations of a cohort study. First, since a cohort is a dynamic phenomenon, with new inclusions, loss of included patients (due to mortality or loss of follow-up), patients temporarily not showing up at the yearly SSc-specific visit, or not yet reaching a specific follow-up visit, the precise number of patients included in the cohort at each moment in time is unpredictable. In order to calculate the cumulative prevalence and incidence, we used as denominator the total number of patients included in the cohort, without taking into account the above-mentioned limitations. This definitely might have underestimated the reported values. Also, since not all patients with normal baseline HRCTs underwent follow-up HRCTs, the incidence rate of ILD may be underestimated. Second, we did not focus on the treatment options and the use of immunosuppressive or immunomodulatory therapy. This is because for ILD in SSc, no disease modifying drugs with long-term efficacy are at hand yet. Also, there might be some bias in the data on the use of immunosuppressive or immunomodulatory therapy, due to the retrospective analysis of the collected data and due to the fact that data were only collected at predefined fixed dates. Also, as this study has been conducted in an era before clinical practice guidelines on treatment of SSc associated ILD were published, for sure not all patients have been treated in that 12 year time period as we would treat them nowadays [19,27,37]. Third, we did not assess the clinical course of ILD in detail. The course of SSc associated ILD remains rather unpredictable [26]. Hence, while of potential interest, we did not investigate which predictors (e.g. antibody state, gender, disease duration, treatment ...) might be associated with progressiveness of ILD, as this research question extends beyond the scope of our very manuscript. Fourth, repeat HRCT was only available in the minority of the patients with ILD at baseline. Follow-up HRCTs were not routinely performed, but according to the current recommendations, only based on clinical examination and PFT changes. We are aware that these small numbers might give a selection bias. Fifth, the HRCTs were only scored as limited or extensive disease by the simplified Goh criteria. HRCT progression was only evaluated from limited to extensive disease and progression within the limited or extensive group was not evaluated. So conclusions on HRCT progression of ILD are outside the purpose of this manuscript. Additionally, one may argue that the Goh algorithm was used for rating ILD by one single investigator. This simplified flow diagram was developed by Goh and colleagues with the aim to enable clinicians with varying expertise to readily classify SSc-ILD patients as "low" or "high" risk [11]. On the one hand, the use of this scoring system could have underestimated the ILD prevalence, as it evaluates only five fixed levels of the HRCT scan. On the other hand, some other lung specific entities resembling lung fibrosis, such as dysaeration of the lung, pneumonitis, post-infectious lesions or post-radiation therapy sequellae, could have been falsely interpreted as ILD. Despite these limitations, the Goh algorithm has already proved its worth in the past for rating ILD in a subgroup of SSc patients with skin involvement (i.e. those SSc patients classified as having either LcSSc or DcSSc), with excellent inter-rater reliability (r=0.81, 95%CI 0.74-0.88) [34]. So, for this manuscript, we chose to rate the HRCTs by one experienced investigator who was blinded to the patient data.

Conclusion

In an unselected, multicentre Flemish SSc cohort, one third has Goh algorithm rated ILD at baseline with an incidence rate of 20.3/1000PY, 95%CI 14.5-27.8, which is in line with current literature. Screening with HRCT at baseline is justifiable both in clinically overt (LcSSc and DcSSc) as well as in the "early" SSc subgroup.

As the majority of the LcSSc or DcSSc patients with ILD at baseline had progression of their ILD during follow-up, yearly routine, rigorous monitoring with PFT seems necessary in these patients.

Frequency of monitoring in the "early" SSc population (with a very low incidence of ILD) might be performed less stringently and may be balanced versus health economy and logistic turn over capacity of local multidisciplinary units.

Funding source declaration

Vanessa Smith is a Senior Clinical Investigator of the Research Foundation – Flanders (Belgium) (FWO) [1.8.029.20N]. The FWO was not involved in study design, collection, analysis and interpretation of data, writing of the report, nor in the decision to submit the manuscript for publication.

Vanessa Smith is supported by an unrestricted educational chair on systemic sclerosis of Janssen-Cilag NV.

This work was supported by an educational grant by Boehringer.

Support for this work was given to Vanessa Smith, by the Fund for Scientific Research in Rheumatology and the Fund Aline, managed by the King Baudouin Foundation.

Statement of author contribution, agreement and declaration

Els Vandecasteele: Substantial contributions to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

Karin Melsens: Substantial contributions to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

Amber Vanhaecke: Substantial contributions to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

Daniel Blockmans: Acquisition of data, critical revision of the intellectual content, final approval of the version to be published.

Carolien Bonroy: Analysis and interpretation of data, critical revision of the intellectual content, final approval of the version to be published.

Charlotte Carton: Input of data (Leuven) in database, critical revision of the intellectual content, final approval of the version to be published.

Ellen Deschepper: Analysis and interpretation of data, critical revision of the intellectual content, final approval of the version to be published.

Filip De Keyser: Acquisition of data, critical revision of the intellectual content, final approval of the version to be published.

Frédéric Houssiau: Critical revision of the intellectual content, final approval of the version to be published.

Yves Piette: Acquisition of data, critical revision of the intellectual content, final approval of the version to be published.

Koen Verbeke: Critical revision of the intellectual content, final approval of the version to be published.

Marie Vanthuyne: Critical revision of the intellectual content, final approval of the version to be published.

Rene Westhovens: Acquisition of data, critical revision of the intellectual content, final approval of the version to be published.

Wim Wuyts: Critical revision of the intellectual content, final approval of the version to be published.

Ellen De Langhe: Acquisition of data, critical revision of the intellectual content, final approval of the version to be published.

Guy Brusselle: Critical revision of the intellectual content, final approval of the version to be published.

Vanessa Smith: Ideation of the study, substantial contributions to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

Declaration of interest

Els Vandecasteele: no conflicts of interest to declare for this study.

Karin Melsens: no conflicts of interest to declare for this study.

Amber Vanhaecke: no conflicts of interest to declare for this study.

Daniel Blockmans: no conflicts of interest to declare for this study.

Carolien Bonroy: no conflicts of interest to declare for this study.

Charlotte Carton: no conflicts of interest to declare for this study.

Ellen Deschepper: no conflicts of interest to declare for this study.

Filip De Keyser: no conflicts of interest to declare for this study.

Frédéric Houssiau: no conflicts of interest to declare for this study.

Yves Piette: no conflicts of interest to declare for this study.

Koen Verbeke: no conflicts of interest to declare for this study.

Marie Vanthuyne: no conflicts of interest to declare for this study.

Rene Westhovens: no conflicts of interest to declare for this study.

Wim Wuyts: no conflicts of interest to declare for this study.

Ellen De Langhe: no conflicts of interest to declare for this study.

Guy Brusselle: no conflicts of interest to declare for this study.

Vanessa Smith: Prof. Smith received a research grant from Boehringer Ingelheim; received an unrestricted educational chair on systemic sclerosis of Janssen-Cilag NV; and received research funding from Actelion Pharmaceuticals Ltd., Bayer AG, F. Hoffman-La Roche AG, Galapagos NV and Sanofi.

Supplementary information

mmc1.docx

Acknowledgements

The Ghent University Hospital is member of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET). The University Hospitals Leuven is member of the European Reference Network on Rare Pulmonary Diseases (ERN LUNG). Both the Ghent University Hospital and the University Hospitals Leuven are members of the Flemish Network on rare connective tissue diseases.

Special thanks goes to Melissa De Decker for her dedication in coordinating daily the logistics of the multidisciplinary care in the Ghent University Scleroderma Unit.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.07.018.

References

[1] Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. Expert Rev Clin Immunol 2019;15(7):753–64.
[2] Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66(7):940–4.
[3] Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76(11):1897–905.
[4] Fischer A, Patel NM, Volkmann ER. Interstitial Lung Disease in Systemic Sclerosis: Focus on Early Detection and Intervention. Open Access Rheumatol 2019;11:283–307.
[5] Trombetta AC, Soldano S, Contini P, Tomatis V, Ruaro B, Paolino S, et al. A circulating cell population showing both M1 and M2 monocyte/macrophage surface markers characterizes systemic sclerosis patients with lung involvement. Respir Res 2018;19(1):186.
[6] Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. Clin Epidemiol 2019;11:257–73.
[7] Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of Pulmonary Complications and Long-Term Survival in Systemic Sclerosis. Arthritis Rheum 2014;66(6):1625–35.
[8] LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger Jr. TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15(2):202–5.
[9] Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.
[10] Rubio-Rivas M, Corbella X, Pestana-Fernandez M, Tolosa-Vilella C, Guillen-Del Castillo A, Colunga-Arguelles D, et al. First clinical symptom as a prognostic factor in systemic sclerosis: results of a retrospective nationwide cohort study. Clin Rheumatol 2018;37(4):999–1009.
[11] Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177(11):1248–54.
[12] Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort. Am J Respir Crit Care Med 2019;200(10):1258–66.
[13] LeRoy EC, Medsger Jr. TA. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28(7):1573–6.
[14] Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008;58(12):3902–12.
[15] Smith V, Vanhaecke A, Herrick AL, Distler O, Guerra MG, Denton CP, et al. Fast track algorithm: How to differentiate a "scleroderma pattern" from a "non-scleroderma pattern". Autoimmun Rev 2019;18(11):102394.
[16] Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev 2020;19(3):102458.
[17] Vandecasteele E, De Pauw M, De Keyser F, Decuman S, Deschepper E, Piette Y, et al. Six-minute walk test in systemic sclerosis: A systematic review and meta-analysis. Int J Cardiol 2016;212:265–73.
[18] Bernstein EJ, Khanna D, Lederer DJ. Screening High-Resolution Computed Tomography of the Chest to Detect Interstitial Lung Disease in Systemic Sclerosis: A Global Survey of Rheumatologists. Arthritis Rheum 2018;70(6):971–2.
[19] Roofeh D, Jaafar S, Vummidi D, Khanna D. Management of systemic sclerosis-associated interstitial lung disease. Curr Opin Rheumatol 2019;31(3):241–9.
[20] Smith V, Scire CA, Talarico R, Airo P, Alexander T, Allanore Y, et al. Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open 2018;4(Suppl 1):e000782.

[21] Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res 2019;20(1):13.
[22] Hoffmann-Vold AM, Allanore Y, Alves M, Graf N, Airo P, Ananyeva LP, et al. Disease course and outcome of progressive interstitial lung disease in systemic sclerosis. Eur Respir J 2019;54:OA3598.
[23] Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airo P, Ananieva LP, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis 2021;80(2):219–27.
[24] Khanna D, Mittoo S, Aggarwal R, Proudman SM, Dalbeth N, Matteson EL, et al. Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) - Report from OMERACT CTD-ILD Working Group. J Rheumatol 2015;42(11):2168–71.
[25] Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-Term Pulmonary Function Trends Are Predictive of Mortality in Interstitial Lung Disease Associated With Systemic Sclerosis. Arthritis Rheum 2017;69(8):1670–8.
[26] Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J 2020:1902026 pii.
[27] Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Distler O, Kreuter M. Evidence-based consensus recommendations for the identification and management of interstitial lung disease in systemic sclerosis. Eur Respir J 2019;54:PA5195.
[28] Hoffmann-Vold A-M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. The Lancet Rheumatology 2020;2(2):e71–83.
[29] Vanthuyne M, Smith V, De Langhe E, Van Praet J, Arat S, Depresseux G, et al. The Belgian Systemic Sclerosis Cohort: correlations between disease severity scores, cutaneous subsets, and autoantibody profile. J Rheumatol 2012;39(11):2127–33.
[30] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72(11):1747–55.
[31] Vandecasteele E, Drieghe B, Melsens K, Thevissen K, De Pauw M, Deschepper E, et al. Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. Eur Respir J 2017;49:1602275 pii.
[32] Van Praet JT, Van Steendam K, Smith V, De Bruyne G, Mimori T, Bonroy C, et al. Specific anti-nuclear antibodies in systemic sclerosis patients with and without skin involvement: an extended methodological approach. Rheumatology (Oxford) 2011;50(7):1302–9.
[33] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37(1):67–119.
[34] Vandecasteele E, Thevissen K, Melsens K, De Keyser F, De Pauw M, Deschepper E, et al. Six-minute walk test in or out in evaluation of systemic sclerosis patients? Clin Exp Rheumatol 2017;106(4):122–9 35 Suppl.
[35] Vandecasteele E, Melsens K, De Keyser F, De Pauw M, Deschepper E, Decuman S, et al. A prospective, longitudinal study evaluating the baseline six-minute walk test as an individual reference value in systemic sclerosis patients. Clin Exp Rheumatol 2018;113(4):95–101 36 Suppl.
[36] Poisson Rate Confidence Interval. Available online from http://www.statsdirect.com/help/rates/poisson_rate_ci.htm Accessed April 5.
[37] Roofeh D, Khanna D. Management of systemic sclerosis: the first five years. Curr Opin Rheumatol, 32; 2020. p. 2020228–37.
[38] Sanchez-Cano D, Ortego-Centeno N, Callejas JL, Fonollosa Pla V, Rios-Fernandez R, Tolosa-Vilella C, et al. Interstitial lung disease in systemic sclerosis: data from the spanish scleroderma study group. Rheumatol Int 2018;38(3):363–74.
[39] Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk AP, et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. Ann Rheum Dis 2009;68(6):961–5.
[40] Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198(5):e44–68.
[41] Smith V, Distler O, Cutolo M. Might Nailfold Capillaroscopy Be a "Proxy" for Lung Involvement in Connective Tissue Diseases? J Rheumatol 2019;46(9):1061–3.
[42] Smith V, Vanhaecke A, Vandecasteele E, Guerra M, Paolino S, Melsens K, et al. Nailfold Videocapillaroscopy in Systemic Sclerosis-related Pulmonary Arterial Hypertension: A Systematic Literature Review. J Rheumatol 2019 pii: jrheum.190296.
[43] Smith V, Vanhaecke A, Guerra MG, Melsens K, Vandecasteele E, Paolino S, et al. May capillaroscopy be a candidate tool in future algorithms for SSC-ILD: Are we looking for the holy grail? A systematic review. Autoimmun Rev 2020;19(9):102619.
[44] Kucharz EJ, Kopec-Medrek M. Systemic sclerosis sine scleroderma. Adv Clin Exp Med 2017;26(5):875–80.
[45] Vandecasteele EH, De Pauw M, Brusselle G, Decuman S, Piette Y, De Keyser F, et al. The heart and pulmonary arterial hypertension in systemic sclerosis. Acta Clin Belg 2016;71(1):1–18.