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Objectives:

To evaluate the baseline clinical characteristics of juvenile systemic sclerosis (jSSc) patients in the international Juvenile SSc Inception Cohort (jSScC), compare these characteristics between the classically defined diffuse (dcjSSc) and limited cutaneous (lcjSSc) subtypes, and among those with overlap features.

Methods:

A cross-sectional study was performed using baseline visit data. Demographic, organ system evaluation, treatment, and patient and physician reported outcomes were extracted and summary statistics applied. Comparisons between dcjSSc and lcSSc subtypes and patients with and without overlap features were performed using Chi-square and Mann Whitney U-tests.

Results:

At data extraction 150 jSSc patients were enrolled across 42 centers, 83% were Caucasian, 80% female, dcjSSc predominated (72%), and 17% of the cohort had overlap features. Significant differences were found between dcjSSc and lcjSSc regarding the modified Rodnan Skin Score, presence of Gottron's papules, digital tip ulceration, 6 Minute walk test, composite pulmonary and cardiac involvement. All more frequent in dcSSc except for cardiac involvement. DcjSSc patients had significantly worse scores for physician rated disease activity and damage. A significantly higher occurrence of Gottron's papules, musculoskeletal involvement and composite pulmonary involvement, and significantly lower frequency of Raynaud´s phenomenon, were seen in those with overlap features.

Conclusion:

Results from a large international jSSc cohort demonstrate significant differences between dcjSSc and lcjSSc patients including more globally severe disease and increased frequency of ILD in dcjSSc patients, while those with lcSSc have more frequent cardiac involvement. Those with overlap features had an unexpected higher frequency of interstitial lung disease.

Significance and Innovations:

1. Juvenile systemic sclerosis (jSSc) patients demonstrate significant differences between dcjSSc and lcjSSc subtype regarding frequency of skin, vascular, pulmonary and cardiac involvement.
2. Physician global assessment of disease activity and damage is higher in the dcjSSc group.
3. jSSc patients with overlap features are not 'protected' from major internal organ involvement and have a higher frequency of lung disease compared to those without overlap features.

Introduction

Juvenile systemic sclerosis (jSSc) is a rare disease with an estimated prevalence of 3 in 1,000,000 children [1]. Only a few publications are available summarizing clinical variables in larger cohorts of these patients (n > 50) [2-6]. Limitations of prior publications include cross sectional data collected retrospectively with chart review across centers [5, 6], or patient data collected before 2006 when clinical evaluation and management was different from the current practice [4-6]. This includes the standardly collected data in the Scalapino cohort (n=111), with patient data collection between 1960-2003 [4]. More recently, there are reports from two prospective registries for jSSc patients: the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry [2] and the juvenile systemic sclerosis inception cohort (jSScC) [3], both with original description of baseline characteristics of n=64 and n=80 jSSc subjects, respectively. One limitation of the recent CARRA cohort was the lack of designation, and therefore description, of limited vs. diffuse cutaneous clinical phenotypes in jSSc.

Overcoming this limitation in our jSScC cohort, organ systems manifestations were extensively captured and compared between limited and diffuse cutaneous subtypes since the extent of skin involvement has been universally accepted to categorize patients with adult onset SSc [7] and has been strongly linked to certain organ manifestations, augmenting patient care guidance [8]. For example, in adult onset SSc with the knowledge that scleroderma renal crisis (SRC) is strongly associated with diffuse cutaneous disease, clinicians will more closely monitor blood pressure in early disease and avoid prednisone when possible since it is a risk factor in developing SRC. An additional categorization of importance in which the frequency of organ manifestations requires further clarification in jSSc is overlap systemic sclerosis. These overlap SSc patients meet classification criteria for SSc but also display overlap features of other connective tissues diseases, such as dermatomyositis [4, 9, 10], and have been reported in higher frequency in prior jSSc cohorts compared to adult SSc [4].

Since the publication of the original manuscript, 70 additional subjects have been enrolled in the jSScC registry and are reported here, with 150 enrolled currently presents the largest jSSc patient cohort, affording the opportunity to make comparisons between clinical and patient reported variables across limited cutaneous, diffuse cutaneous and overlap systemic sclerosis in juvenile onset disease. This enables us to build upon the original manuscript comparing diffuse and limited cutaneous clinical features, as well as providing the first study in jSSc to systematically compare jSSc patients with and without overlap features. Our overall objective is to determine if there are important associations of organ involvement

and patient impact among these subtypes, which may ultimately influence patient evaluation and monitoring.

Methods

The jSScC registry cohort, as previously described [3], is an international prospective observational cohort study, including 25 centers from Europe, 5 from Asia, 6 from North America and 6 from South America, representing 42 academic institutions. All participating centers had the research protocol approved by their local Ethics Committee. We are presenting a cross sectional analysis of the data obtained at the patients' baseline cohort visit.

The jSScC registry inclusion criteria required fulfilling classification criteria of SSc, using the more strict pediatric provisional 2007 classification [11] criteria from January 2008 – September 2017, and after an amendment from October 2017, modifying this criteria the more inclusive 2013 ACR/EULAR adult classification criteria for systemic sclerosis [12], which allows for earlier detection of disease with gaining points for sclerodactyly and not requiring the progression of skin thickness beyond the MCPs, which was a limitation of the preliminary pediatric classification criteria in the authors opinion (IF and KT). The other criteria were unchanged throughout the study, and include the following: age of less than 16 years old at the time of the first non-Raynaud sign of disease, and less than 18 years old at the time of the enrollment.

Data collection from jSSc patients includes demographic, physical examination, clinical testing variables, and physician and patient related outcome measures as described in the original publication of the first 80 subjects [3] *(Supplementary material includes the clinical research form (CRF) obtained at the visits)*. Patients were scored for the presence and degree of skin thickness by the modified Rodnan skin score [13] and cutaneous involvement was classified into diffuse and limited subtype, with diffuse cutaneous (dc) defined by widespread and rapidly progressive skin thickening (starting at fingers and toes and spreading proximal beyond elbows and knees) and limited cutaneous (lc) characterized by restricted and non-progressive skin thickening (starting at fingertip and toes but limited to distal extremities, not crossing antecubital or popliteal fossa) [7]. Overlap subset of jSSc was not collected independently, rather overlap features were collected among the dcjSSc and lcjSSc patients, including variables such as Gottron's papules, myositis, arthritis, and sicca symptoms.

In addition to the variables listed in our prior publication [3] we created a 'composite pulmonary involvement' variable, defined as meeting at least one of the following criteria: forced vital capacity (FVC)

< 80% of the predicted value; diffusing capacity for carbon monoxide (DLCO) < 80%; or high-resolution computed tomography (HRCT) findings consistent with interstitial lung disease (ILD). Moreover, digital ulcers were quite common in our initial cohort assessment [3] and have an impact on daily life in our jSSc patients [2, 14], therefore we have incorporated the DUCAS score [15] as an outcome variable collected prospectively. Data was collected prospectively according to a standardized assessment protocol every 6 months *(see Supplement CRF)*.

Statistics

Data were extracted for patients enrolled from January 2008 to December 15, 2019. Only baseline visit enrollment data were analyzed for this report. Statistical analyses were conducted using SAS software version 9.4. Categorical variables were reported by absolute and relative frequencies and continuously distributed variables by median and interquartile range (25^{th} and 75^{th} percentile). Comparisons between patients with diffuse and limited cutaneous involvement and those with and without overlap features were performed using chi-square test and Fisher's exact when appropriate for categorical variables and Mann Whitney U-test for continuously distributed variables. A p value of <0.05 was considered to be statistically significant.

Results

Patient Demographics, Autoantibody and Laboratory Findings.

At the time of data query, 150 patients were enrolled in the jSScC cohort across the 42 academic institutions, with the majority being Caucasian (83%) and female (80%) (Table 1). All patients who fulfilled the pediatric SSc classification criteria [11], fulfilled the adult SSc criteria [12], which was applied for the inclusion since October 2017. Ninety-seven patients in this cohort were included before the amendment. The diffuse cutaneous subtype was predominant (72%), compared to lcjSSc (28%). Overlap features were present in 17% of the cohort with higher frequency in lcjSSc compared to dcjSSc (n=12, 28% vs. n=14, 13%; p=0.023). Although slightly younger in the dcjSSc group compared to lcjSSc, the median age of onset at Raynaud and first non-Raynaud symptom was not significantly different between the cutaneous subtypes 10.3 vs. 11.9 years and 10.7 vs. 13.1 years old, respectively. Median disease duration at time of enrollment was 2.6 years in the dcjSSc and 1.8 years in the lcjSSc group (p=0.038). The majority (81%) of jSSc patients were being treated with disease modifying agents, regardless of subtype (Table 1). Evaluation of auto-antibodies supports ANA positivity in 91% of the cohort with a similar distribution of antibodies against extractable nuclear antigens (Scl-70 and centromere), between the two cutaneous subtypes, reflecting the findings from the original 80

patients described [3]. Specifically, anti-Scl-70 positivity was found in approximately one-third of the cohort (35% in dcjSSc vs. 36% in lcjSSc) and anti-centromere positivity was found at a very low rate of in both subsets (3% vs. 7%, respectively) (Table 1). Anti-PM-Scl antibody, reflecting overlap disease, was similarly present in dcjSSc and lcjSSc (14% and 20% respectively), with higher frequency in those with overlap compared to those without (31% vs. 10%, respectively, p=0.046) (Table 4). Additional comparison of laboratory evaluation included inflammatory markers, such as erythrocyte sedimentation rate, which was elevated in 29% in the dcjSSc and 16% in the lcjSSc (p=0.107). C Reactive Protein elevation was less frequently encountered, 15% in the dcjSSc and 9% in the lcjSSc (p=0.40) (Table 1). The patients with overlap features had similar frequencies as the dcjSSc for these variables (Supplemental Table 1).

Clinical Features.

The summary of clinical features in the total cohort and between diffuse and limited cutaneous subtype are presented in Table 2. Several organ system outcomes had a more frequent occurrence in the dcjSSc subset compared to the lcjSSc patients, with significant differences in the median modified Rodnan skin score (17.0 in the dcjSSc vs. 4.5 in the lcjSSc; p<0.001), sclerodactyly (83% vs. 66%; p=0.029) and Gottron´s papules (30% versus 13%; p=0.043) for cutaneous organ involvement.

Regarding microvascular involvement, Raynaud phenomenon was similar in both subgroups (approximately 90%), but presence of telangiectasia was more frequent in the dcjSSc (42% vs. 18%; p=0.01), as well as history of ulceration (56% versus 32%; p=0.008). The DUCAS score [15] reflecting ulceration severity, did not statistically significant differ (p=0.147) between dcjSSc patients (median 0 (IQR 0 – 0.25)) compared to 0 (0 – 0) (Table 2). However, about 80% (46 of 58) of patients had a DUCAS score of zero (lcjSSc 93% versus dcjSSc 75%).

Cardiopulmonary assessment demonstrated some differences between cutaneous subtypes, with more pulmonary morbidity in the dcjSSc group and more cardiac morbidity in the lcjSSc group (Table 2). The pulmonary parameters were more frequently abnormal in the dcjSSc subtype, including FVC <80%, DLCO <80%, and ILD findings on HRCT. Although not statistically significant individually, combining these factors in the composite pulmonary involvement variable, dcjSSc demonstrated more pulmonary involvement than lcjSSc in a statistical and clinically significant manner (49% vs. 31%; p=0.045). In accordance with this finding, the 6 Minute walk test was more frequently below the 10^{th} percentile in dcjSSc (85% vs. 54%; p=0.044). Cardiac involvement overall was relatively infrequent in the cohort (6%), but when it occurred it was more frequent in the lcjSSc group (17% vs. 2%; p=0.002). The majority

of patients did have cardiac screening with electrocardiogram conducted in 80% of the patients (78% in dcjSSc and 86% in lcjSSc) and transthoracic echocardiogram in 64% of the patients (62% in dcjSSc and 69% in lcjSSc). Cardiac involvement was described in five patients with arrhythmia, one with tricuspid insufficiency and one with mitral regurgitation in the lcjSSc group, and both patients in the dcjSSc group with arrhythmia. Pulmonary hypertension, screened by transthoracic echocardiogram, according to the pediatric guidelines [16, 17], was uncommon and similar in both groups (dcjSSc n=7, 6%; lcjSSc n=2, 5%) (Table 2). Primary vs. secondary pulmonary arterial hypertension (PAH) was not designated by the treating physician in the CRF, but the status of ILD was recorded. Of the 9 patients with PAH, 3 of the 7 in dcSSc and 1 of the two in the lcSSc had no associated signs of ILD, therefore 44% (4/9) of those with PAH would likely be designated as primary.

No history of renal crisis was detected at time of enrollment in the cohort and only one patient had arterial hypertension in the lcjSSc group. In the dcjSSc group five patients had proteinuria, 4 of them less than 500 mg/day and the fifth 1.1 g/day. A renal biopsy was performed on the dcjSSc patient with significant proteinuria and Class V lupus nephritis was identified, we considered this as an overlap feature. In the lcjSSc group, one patient had microscopic hematuria and proteinuria less than 500 mg/day and other patient had isolated microscopic hematuria.

Gastrointestinal involvement occurred in 42% in the dcjSSc patients and 29% in the lcjSSc patients (p=0.138). Esophageal involvement was the most frequent manifestation in both groups, which occurred in 39% in the dcjSSc and in 29% in lcjSSc (p=0.898) (Table 2).

Muscle weakness occurred in 18% in dcjSSc and 31% in lcjSSc patients (p=0.132). In patients with overlap features in both subsets 45% had muscle weakness. Tendon friction rub was infrequent and in the same range in both groups (9% in dcjSSc and 6% in lcjSSc; p=0.54). Joint contractures were observed in 48% in dcjSSc and 43% in lcjSSc patients (p=0.630), and swollen joints were observed in 21% in dcjSSc and 17% of lcjSSc (p=0.630) (Table 2). Neurologic involvement was seldom (3% of the cohort) and was most commonly associated with musculoskeletal entrapment, with all 3 dcSSc with neurologic involvement having Carpal tunnel syndrome, while the two lcSSc patients with neurologic involvement were more divergent, with one having demyelinating sensorimotor axonal polyneuropathy and the other with headache.

Global Assessments – physician and patient reported.

Patients with dcjSSc had significantly worse scores for Physician Global Assessment of disease activity compared to lcjSSc patients (VAS scale 0-100) (median 37.5 versus 20; p=0.002) and for Physician Global Assessment of disease damage (VAS scale 0-100) (median 30 versus 10; p<0.001) (Table 3). Physician rated ulceration activity was in the similar range (VAS 0-100) (median 5 versus 0; p=0.113). There was no statistically significant difference in the patient rated global disease activity, global disease damage, Raynaud´s activity and ulceration activity on a VAS (0-100) between diffuse and limited cutaneous subtypes. The mean score in the Childhood Health Assessment Questionnaire (CHAQ) was 0.5 in the dcjSSc, 0.4 in the lcjSSc subjects (p=0.707; Table 3) and 0.7 in those with overlap (Table 4 and Supplemental Table 2).

Patients with Overlap Features

Overlap features occurred in 17% (26/150) of all jSSc patients, 13% in the diffuse cutaneous subtype group and 28% in the limited cutaneous subtype group (Table 2). Those with overlap features had similar demographics (sex, race, disease onset and duration; Supplemental Table 1) as those without but did have some notable clinical differences. Overlap patients showed characteristics of dermatomyositis in 23 cases, one combined with Sjögren Syndrome, and three had juvenile arthritis characteristics. More frequent cutaneous and musculoskeletal manifestations in patients with overlap features include Gottron's papules, number of joints with swelling, decreased range of motion, joint contractures, and muscle weakness (Table 4, Supplemental Table 2). Vascular features, such as Raynaud phenomenon occurred more commonly in the non-overlap group (93 vs. 77%; p=0.015; Supplemental Table 2). Digital ulcer frequency was similar between those with and without overlap features (Supplemental Table 2). Interstitial lung disease appeared more prevalent in those with overlap features, with the composite pulmonary involvement variable, DLCO <80% and abnormal findings on HRCT, was significantly more common in this group (61 vs. 40%, p=0.048); Table 4, Supplemental Table 2). The uncommon organ systems involved in jSSc, including cardiac, renal and neurological, were similar in those with and without overlap features (Supplemental Table 2). The overlap patients most commonly had positive ANA without a specific extractable nuclear antigen, followed by positive PM-Scl (31%) and Scl-70 (12%), with no patients with a positive anti-centromere antibody (Table 4; Supplemental Table 3). Physician and patient reported outcomes were not significantly different between those with and without overlap characteristics, besides patient rating of the Raynaud's activity, which was significantly higher in the non-overlap patients (30 vs. 2.5, p=0.044; Table 4, Supplemental Table 3). Although not statistically significant, the CHAQ was more impacted in the overlap patients compared to non-overlap patients (0.7 vs. 0.5, p=0.097; Table 4, Supplemental Table 3).

Discussion

We present the largest cohort of jSSc patients with prospectively collected standardized clinical assessment. It is reassuring that the unique findings that we described in our previous publication of this cohort [3], regarding the dominance of the dcjSSc subtype and the unique distribution of the antibody pattern, are further confirmed. The additional 70 patients enrolled since the prior publication (n=150 vs. 80) allows for the identification of additional cutaneous and vascular differences between dcjSSc and lcjSSc patients, in addition to enabling the characterization of overlap SSc patients. Patients with dcjSSc have, as expected by definition, higher mean modified Rodnan skin scores, but they also have significantly higher rate of cutaneous and vascular features: sclerodactyly, Gottron's papules, history of ulceration and presence of telangiectasia. It was surprising that telangiectasias were not predominant in the limited cutaneous subtype as one might expect in the classic teaching of CREST syndrome in adult onset SSc, which clinical phenotype is consistent with lcSSc [18]. One possible explanation is the disease duration on average was one year longer in the dcjSSc subjects allowing more time for telangiectasias accumulate, and that the lcjSSc subjects may approach a similar frequency with longer follow-up analyses (underway). As demonstrated in our earlier manuscript, dcjSSc patients have a significantly higher rate of pulmonary involvement, evaluated using a composite item or the 6 Minute walk distance test. Cardiac involvement, although rare, is a major cause of morbidity in jSSc, and confirming our earlier publication, was significantly higher in the lcjSSc group, and therefore deserves particular attention in this cutaneous subtype. Overall disease severity, gauged by the physician global assessment of disease activity and damage, supports more impact on those with dcjSSc patients, whom tend to have cumulative higher total organ morbidity. Efforts to decrease this cumulative burden are underway with the more liberal use of disease modifying agents in SSc earlier on in the disease process in both adult and pediatric-onset SSc [19-21].

In contrast to adult-onset SSc cohorts comparing large numbers of diffuse and limited cutaneous patient subsets, such as the EUSTAR database and the Patient-Centered Intervention Network Cohort (SPIN), we did not find the increased frequency of the following variables in dcjSSc that were demonstrated in adult dcSSc: male patients, positive Scl-70, renal crisis, joint contractures, tendon friction rub and functional impairment [8, 22] [23]. Similar frequency of clinical manifestations between the adult cohorts and our jSSc cohort was the finding of more frequent pulmonary involvement in the diffuse subset. A main overall difference between our jSSc cohort and these large adult SSc cohorts is the overall percentage of limited compared to diffuse cutaneous, in which lcSSc

predominates in adults (60%) and dcSSc in our jSSc cohort (72%). One explanation for this difference may be the significantly longer disease duration upon cohort entry, with 11.7 years from the first non-Raynaud in the SPIN cohort and 6.4 years for lcSSc and 4.2 years for dcSSc in the EUSTAR cohort, allowing the capture of more lcSSc patients. This is in comparison to the median disease duration of 2.6 years in the diffuse subtype and 1.8 years in the limited subtype in our jSSc cohort, which are relatively short in disease duration contrasted to adult onset, and are similar in timing. The jSScC cohort has been enrolling over the past 10 years and this diffuse cutaneous predominance persists, supporting we are likely not necessarily missing the late bloomer lcSSc, but indeed pediatric onset patients have a unique subset distribution at the beginning of the disease and a unique organ pattern presentation.

Overlap features occurred in 17% of the patients in our pediatric cohort, with the vast majority of the patients (88%) with dermatomyositis overlap, the few others with Sjögren syndrome (n=1) and juvenile arthritis (n=3) overlap. The general percentage of overlap SSc subtype in adult onset SSc cohorts ranges from approximately 5 to 20%, and includes overlap with the following connective tissue diseases (CTD): Sjogrens, polymyositis/dermatomyositis, rheumatoid arthritis, and systemic lupus erythematous, with varying dominant CTD among published cohorts, though dermatomyositis and systemic lupus were noted in the younger adult age onset (16-40 years old) compared to older adult onset (40 years+) [4, 25-27]. Another jSSc cohort which categorized overlap patients (n= 32/110; 29%) also found juvenile dermatomyositis to heavily predominate with 72% (23/32) [4] similar to our jSScC cohort findings. The most notable finding in our overlap patients is the higher risk for interstitial lung disease compared to those without overlap features, with abnormal DLCO and HRCT being more common in this subgroup. This is important as it contradicts some more traditional teaching [27] that those with overlap disease possess a less severe phenotype, and instead should prompt clinicians to be on higher alert for ILD and internal organ manifestations, not only focused on musculoskeletal, vascular and cutaneous involvement. A recent study in a large German cohort of 3,240 adult onset SSc specifically examined their registry patients with SSc-overlap syndrome (10%; n=325) and evaluated their organ frequency as well as trajectory and found the patients with overlap syndromes had a higher risk of developing lung fibrosis and heart involvement compared to lcSSc, though less than dcSSc, and harbor an intermediate rate of cardiopulmonary progression between lcSSc and dcSSc [26]. We are collecting longitudinal data to further study jSSc overlap subtype trajectory compared to non-overlap dcSSc and lcSSc. Those with overlap features indeed, may be at risk for poorer outcomes and overall well-being. There does appear to be a significant impact on physical functioning in our patients with jSSc overlap defined by the CHAQ. The mean CHAQ score of 0.7 in those with overlap features is higher than the mean CHAQ

reported in the CARRA legacy registry cohort for juvenile onset SLE (0.26), dermatomyositis (0.41), and juvenile arthritis (0.38) [2], which is most likely clinically relevant given the general floor effect of the CHAQ with low total score of 0-3.

Limitations in our study including missing data. Despite the use of a standardized assessment protocol, this is an observational cohort in which participating clinicians report according to their standard of care in jSSc. Assessment of antibodies was the physician's discretion and possibility of the health system to assess them in the routine care, the lack of testing for all subjects could have influenced our interpretation. Performance of additional organ evaluation, such as esophageal manometry, was not mandatory due to the observational study design and ethical reasons. In consequence, the results of specific organ manifestation screenings included a proportion of missing data and may be slightly biased to patients with a more severe organ involvement, but the stability of the observed organ involvement pattern between the publication of the 80 and now the 150 patients is reassuring. Another limitation is the cross-sectional analysis of our cohort at cohort entry. Therefore, all results have to be interpreted with caution and no causal inference should be drawn from our results.

In conclusion, we present the largest jSSc patient population with a prospectively collected standardized assessment. The unique findings that we had previously published summarizing 80 patients of the cohort [3] persist with the increased cohort size (n=150) and similar to the other large published cohorts [2, 4, 5]. A few differences exist between dcjSSc and lcjSSc in children, such as increased frequency of ILD in dcjSSc and cardiac involvement in lcjSSc, which should be noted for clinical screening and monitoring evaluation. Additionally, analyses of those with overlap features demonstrated expected cutaneous and musculoskeletal involvement, but unexpected increased frequency of interstitial lung disease. Future, longitudinal study of this cohort will determine if dcjSSc and lcjSSc subtype, and those with overlap features retain these organ manifestations or follow a different trajectory. Medications are also captured at every visit and will be documented in the longitudinal evaluation to query relationships between medication regimen and organ systems outcomes while awaiting traditional clinical trials in jSSc, which are difficult due to the rarity of disease. In addition to clinical phenotype, future collection of molecular markers in tandem may assist in further immunophenotype classification as being evaluated in adult onset SSc [28, 29].

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Table 1. Demographic, disease characteristics, autoantibody and laboratory measures of the 150 juvenile systemic sclerosis patients in the cohort, compared by cutaneous subtype.

	Whole Group **N=150**	**Diffuse Subtype** **N=108**	**Limited Subtype** **N=42**	**Comparison between diffuse and limited subtypes** **P value**
Female to Male Ratio	4.2:1 (121/29)	4.1:1 (87/21)	4.2:1 (34/8)	0.571
Race				0.871
Caucasian	83% (124)	83% (90)	81% (34)	
African	6% (9)	7% (8)	2% (1)	
Indian	6% (9)	3% (3)	14% (6)	
Other	5% (8)	6% (7)	2% (1)	
Disease duration (years), median (IQR)	2.4 (0.9 – 4.4)	2.6 (1.3 – 4.8)	1.8 (0.6 – 4.1)	0.038
Age at onset of Raynaud´s (years), median (IQR)	10.8 (6.9 – 13.1)	10.3 (7.0 – 12.8)	11.9 (6.3 – 13.9)	0.139
Age at onset of non-Raynaud´s (years), median (IQR)	11.1 (6.9 – 13.5)	10.7 (7.0 – 12.7)	13.1 (6.8 – 14.5)	0.091
Disease modifying drugs	81% (122)	80% (86)	86% (36)	0.390
Autoantibody positivity:				
ANA	91% (133/146)	91% (95/104)	90% (38)	0.867
Anti-Scl 70	35% (51/145)	35% (36/103)	36% (15)	0.930
Anti-centromere	4%	3%	7%	0.370

	(4/97)	(2/68)	(2/29)	
Anti-PMScl	16% (9/57)	14% (5/37)	20% (4/20)	0.522
Laboratory values:				
ESR elevated (>20 mmHg)	25% (36/141)	29% (30/103)	16% (6/38)	0.107
CRP elevated (>5 mg/l)	13% (17/127)	15% (14/94)	9% (3/33)	0.400
Elevated CK	22% (23/102)	26% (19/72)	13% (4/30)	0.151
Elevated CK in overlap patients	9% (2/23)	8% (1/13)	10% (1/10)	0.846
Pro-BNP increased	23% (4/17)	23% (3/13)	15% (1/4)	0.937

IQR: interquartile range , 25^{th}-75^{th}%; ANA: Anti-nuclear antibody; Scl: Scleroderma; PMScl: Polymyositis-Scleroderma; ESR: erythrocyte sedimentation rate; CRP: C-reactive Protein; CK: Creatine kinase; BNP: B-type natriuretic peptide

Table 2. Clinical manifestations of the 150 juvenile systemic sclerosis patients in the cohort, compared by cutaneous subtype.

	Whole Group N=150	**Diffuse Subtype N=108**	**Limited Subtype N=42**	**Comparison between diffuse and limited subtypes P value**
Overlap features	17% (26)	13% (14)	28% (12)	**0.023**
Cutaneous:				
modified Rodnan skin score, median (IQR)	12.5 (5 – 22.5)	17 (9 – 27)	4.5 (0 – 10)	**<0.001**
Gottron Papules	26% (37/142)	30% (32/105)	13% (5/37)	**0.043**

Gottron papules in overlap patients	48% (11/23)	82% (9/11)	17% (2/12)	**0.002**
Puffy Fingers	31% (39/126)	32% (29/90)	28% (10/36)	0.626
Sclerodactyly	78% (108/138)	83% (83/100)	66% (25/38)	**0.029**
Vascular:				
Raynaud´s phenomenon	90% (135)	91% (98)	88% (37)	0.628
Nailfold capillary changes	72% (101/141)	71% (70/99)	74% (31)	0.709
Telangiectasia	44% (56/128)	42% (38/90**)**	18% (7/38)	**0.010**
History of ulceration	49% (73/148)	56% (60/107)	32% (13/41)	**0.008**
Active ulceration	15% (22/148)	16% (17/107)	12% (5/41)	0.572
DUCAS score, median (IQR)	0 (0 – 0)	0 (0 – 0.25)	0 (0 – 0)	0.147
Calcinosis	17% (11/64)	21% (10/48)	6% (1/16)	0.181
Pulmonary:				
FVC < 80%	31% (33/106)	35% (27/78)	21% (6/28)	0.196
DLCO < 80%	44% (31/71)	44% (22/50)	43% (9/21)	0.929
Abnormal findings on HRCT	42% (46/110)	45% (37/82)	32% (9/28)	0.229
6 Minute Walk Test under the normal range (<10 Percentile of normal range)	76% (29/38)	85% (23/27)	54% (6/11)	**0.044**
Composite Pulmonary Involvement	44% (66)	49% (53)	31% (13)	**0.045**
Cardiac:				
Cardiac Involvement	6% (9)	2% (2)	17% (7)	**0.002**

Pulmonary Hypertension assessed by US	6% (9)	6% (7)	5% (2)	0.691
Renal:				
Renal Involvement assessed by urinalysis	5% (7)	5% (5)	5% (2)	0.972
Hypertension assessed by RR	1% (1)	0% (0)	2% (1)	0.108
Renal Crisis	0% (0)	0% (0)	0% (0)	-
Gastroenterology:				
Total Gastrointestinal Involvement	38% (57)	42% (45)	29% (12)	0.138
Total Oesophageal Involvement	36% (54)	39% (42)	29% (12)	0.898
Musculoskeletal:				
Overall	62% (92/149)	62% (66/107)	62% (26)	0.929
Presence of swollen joints	19% (29/149)	21% (22/107)	17% (7)	0.606
Presence of joints with decreased range	54% (81/149)	56% (60/107)	50% (21)	0.540
Presence of joints with pain on motion	23% (35/149)	21% (22/107)	31% (13)	0.169
Contractures	47% (69/148)	48% (51/106)	43% (18)	0.630
Muscle Weakness	22% (27/124)	18% (17/92)	31% (10/32)	0.132
Muscle weakness in overlap patients	45% (10/22)	45% (5/11)	45% (5/11)	-
Tendon Friction Rub	8% (11/139)	9% (9/103)	6% (2/36)	0.543
Neurological Involvement:				
Overall Neurological involvement	3% (5)	3% (3)	5% (2)	0.543

FVC: functional vital capacity; DLCO : diffusion capacity of carbon monoxide; US: ultrasound; RR:assessed by Riva Rocci method; IQR: interquartile range, 25^{th}-75^{th}%

Table 3. Patient and physician related outcomes of the 150 juvenile systemic sclerosis patients in the cohort, compared by cutaneous subtype.

	Whole Group **N=150**	**Diffuse Subtype** **N=108**	**Limited Subtype** **N=42**	**Comparison between diffuse and limited subtypes** **P value**
Physician Reported* (median, IQR)				
Physician global disease activity	30 (20 – 50) n=116	37.5 (25 – 50) n=88	20 (10 – 32.5) n=28	**0.002**
Physician global disease damage	30 (15 – 45) n=115	30 (20 – 50) n=88	10 (5 – 25) n=27	**<0.001**
Physician ulceration activity	0 (0 – 20) n=136	5 (0 – 20) n=104	0 (0 – 12.5) n=32	0.113
Patient Reported* (median, IQR)				

Patient global disease activity	40 (30 – 60) n=106	40 (30 – 55) n=86	50 (22.5 – 60) n=20	0.964
Patient global disease damage	40 (20 – 60) n=105	40 (20 – 60) n=85	47.5 (5 – 60) n=20	0.424
Patient Raynaud activity	25 (5 – 55) n=130	30 (10 – 55) n=102	15 (0 – 50) n=28	0.159
Patient ulceration activity	5 (0 – 30) n=131	7.5 (0 – 30) n=102	0 (0 – 25) n=29	0.242
CHAQ	0.25 (0 – 0.75) n=94	0.25 (0 – 0.63) n=68	0.25 (0 – 0.75) n=26	0.707
CHAQ, mean (range)**	0.5 (0 – 2.6)	0.5 (0 – 2.6)	0.4 (0 – 2)	0.707

All Physician and patient reported measures are VAS scales 0-100mm (min-max) ; IQR: interquartile range, 25^{th}-75^{th}%; CHAQ: Child Health Assessment Questionnaire

**mean also presented to be able to compare to other published pediatric rheumatic disease group data

Table 4. Main differences of between clinical manifestations of the 150 juvenile systemic sclerosis patients in the cohort, compared by overlap features.

	Patients without overlap N=124	Patients with overlap N=26	Comparison between with/without overlap P value
Autoantibody positivity:			
Anti-Scl 70	40% (48/120)	12% (3/25)	**0.008**
Anti-centromere	5% (4/81)	0% (0/18)	0.336
Anti-PMScl	10% (4/41)	31% (5/16)	**0.046**
Cutaneous:			
Gottron Papules	21% (26)	48% (11/23)	**0.022**
Pulmonary			
Composite Pulmonary Involvement	40% (50)	61% (16)	**0.048**
Renal:			
Renal Involvement assessed by urine test	4% (5)	8% (2)	0.421
Musculoskeletal:			
Presence of swollen joints	14% (18)	42% (11)	**0.001**
Muscle Weakness	17% (17/102)	45% (10/22)	**0.003**
Tendon Friction Rub	6% (7/114)	16% (4/25)	0.098
Patient Reported			
Patient Raynaud's activity, median (IQR)	30 (10 – 55), n=108	2.5 (0 – 40), n=22	**0.045**
CHAQ, median (IQR)	0.25 (0 – 0.63) n=75	0.5 (0 – 1), n=19	0.097
CHAQ mean (range)*	0.5 (0 - 2.6)	0.7 (0 – 2.5)	0.097

Scl: Scleroderma; PMScl: Polymyositis-Scleroderma; CHAQ: Child Health Assessment Questionnaire; IQR: interquartile range , 25^{th}-75^{th}%

*mean also presented to be able to compare to other published pediatric rheumatic disease group data