This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ACR.24499

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Word Count: 3,307
Tables: 1
Figures: 2
Supplementary Tables: 6

Financial support: No financial support or other benefits from commercial sources were obtained for the work reported in the manuscript. There is no financial conflict of interest of any of the authors. The inception cohort project is supported by an unrestricted grant from the Joachim Hertz Stiftung, Hamburg, Germany.
Objectives
Utilizing data obtained from a prospective international juvenile systemic sclerosis cohort (jSScC) to determine if pulmonary screening with forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) is sufficient to assess the presence of interstitial lung disease (ILD) in comparison to high resolution computed tomography (HRCT) in jSSc.

Methods
The jSScC cohort database was queried for patients enrolled from January 2008 to January 2020 with recorded pulmonary function tests (PFT) parameters and HRCT to determine the discriminatory properties of PFTs parameters, FVC and DLCO, in detecting ILD.

Results
Eighty-six jSSc patients had both CT imaging and FVC values for direct comparison. Using findings on HRCT as the standard measure of ILD presence, the sensitivity of FVC in detecting ILD in jSSc was only 40%, the specificity was 77%, and AUC was 0.58. Fifty-eight jSSc patients had both CT imaging and DLCO values for comparison. The sensitivity of DLCO in detecting ILD was 76%, the specificity was 70%, and AUC was 0.73.

Conclusion

The performance of PFTs in jSSc to detect underlying ILD was quite limited. Specifically, the FVC, which is one of the main clinical parameters in adult SSc to detect and monitor ILD, would miss approximately 60% of children that had ILD changes on their accompanying HRCT. The DLCO was more sensitive in detecting potential abnormalities in HRCT, but with less specificity than the FVC. These results support the use of HRCT in tandem with PFTs for the screening of ILD in jSSc.

Significance and Innovations

In a large international prospective cohort of children with a rare condition, juvenile systemic sclerosis (jSSc), data comparing pulmonary function tests (PFTs) with high resolution computed tomography (HRCT) of the chest to detect interstitial lung disease (ILD) found:

- The discriminatory properties of forced vital capacity (FVC) to have low sensitivity, which would miss ILD in approximately 2/3 of the jSSc cohort patients.
- The discriminatory properties of the diffusion capacity of the lungs for carbon monoxide (DLCO) had better sensitivity but lower specificity.
- When FVC and DLCO are combined, discriminatory properties are improved, but only when they both are above or below the traditional 80% cut off, which negates several patients that have values that are on conflicting sides of the cut offs for the two PFT values.

Given these limitations of discriminatory properties of PFTs alone in the detection of ILD, which is prevalent in jSSc (affecting 44% of the international cohort), physicians should ascertain the presence of ILD with the combination of HRCT and PFT in jSSc patients.
Introduction

Juvenile systemic sclerosis (jSSc) is an orphan disease with a prevalence of approximately 3 in a million children, and due to this paucity of cases, most general guidelines of care and treatment from pediatric rheumatologist are based on adult onset SSc experience[1]. Interstitial lung disease (ILD) is a major cause of morbidity for both adult and juvenile-onset SSc (Figure 1), occurring in approximately 35-55 % of patients in published jSSc cohorts [2, 3]. Currently, novel medications which can attenuate inflammatory driven lung fibrosis are being tested in clinical trials of adult SSc patients with ILD. Resulting from these trials, are medications such as nintedanib, an inhibitor of platelet-derived growth factor receptor (PDGFR)-α and β, which has been recently licensed for SSc-associated ILD [4] and a pediatric study is planned (EMEA-001006-PIP05-18). Responsiveness to such medication relies on early recognition of ILD in order to minimize fibrotic load and prevent more permanent tissue damage.

Screening for ILD in adult and pediatric SSc patients traditionally includes pulmonary function tests (PFT), specifically spirometry and single breath diffusion capacity for carbon monoxide (DLCO) at a minimum [5]. This allows the detection of a restrictive lung defect (low FVC and restricted pattern on flow volume loop) with associated decreased DLCO, reflecting the thickened interstitium from ILD (after parenchymal inflammation and fibrosis) [6-9]. Assessment of FVC is fairly standardized from the age of 3 years, with a grading system for the quality of the test session starting at the age of 2 years [10-12]. Following FVC and DLCO PFT values in a serial manner in adult SSc has proven to be helpful as a biomarker reflecting lung disease status, with a change of 10% in FVC and 15% in DLCO regarded as clinically meaningful [6, 8, 9, 13]. However, PFT measurements are limited in detecting earlier lung disease in SSc. This has been recognized in both children and adults since measurements of FVC and DLCO are associated with considerable variability due to technical factors, diurnal or seasonal variability, or patient related factors separate from true pathophysiological changes. A specific technical example in SSc is the ability to fully make a seal on the mouthpiece to obtain accurate readings, often, with tight facial skin and limited oral aperture, this is not possible. The use high resolution computed tomography (HRCT) has become the mainstream imaging modality for screening and quantifying ILD in adults [5, 7, 8, 13] with the combination of HRCT imaging and PFT to both detect and follow ILD progression and regression [6, 8].
In children, traditionally, PFT have been used for ILD screening, with the more guarded use of HRCT for concerns of radiation in children, being reserved for the more symptomatic jSSc patients or for those with abnormal FVC and/or DLCO values (<80% ) (predicted for age, weight, height, sex, and race) [10, 11, 14]. The decreased amount of radiation used in HRCT recently [14]; the evidence from adult SSc of HRCT being more sensitive for earlier ILD [7]; the number of “asymptomatic” children who tend to subconsciously self-limit physical activity of more rigorous exercise to avoid dyspnea; and the poor reliability of the DLCO in children less than 8 years of age [10-12], all support the more current practice of using HRCT in tandem with PFT for ILD screening in jSSc. This reflects the more recent management style of pediatric rheumatologists enrolling patients into the international juvenile systemic scleroderma cohort (jSScC). Therefore, we reviewed the data collected from our prospective international cohort to evaluate the performance parameters of PFT in context with concurrently collected HRCT.

Patients and Methods

The international inception cohort for patients with jSSc (jSSC) is a large multicenter observational study, including 25 centers from Europe, 5 from Asia, 6 from North America and 6 from South America, representing 42 academic institutions [2]. The cohort includes patients with a definite diagnosis of jSSc who are less than 18 years old at enrollment. The rheumatologist is requested to report at enrollment (baseline) and every 6 months clinical characteristics, exam findings, laboratory values, evaluations and treatment related to jSSc management by a standardized case report form. In addition, physician and patient reported outcomes of global disease activity and damage are collected. Lung specific data collection includes PFT parameters (FVC, DLCO), which are reported as percentage of the predicted value for the patient’s demographics. A cut off value of <80% (predicted for age, weight, height, sex, and race) is used to determine an abnormal FVC and DLCO as defined as a traditional threshold in healthy children [10-12]. Abnormal findings of HRCT examinations were recorded, and findings such as ground glass opacities, reticulations and honeycombing, consistent for ILD, were used to define the presence of ILD [8]. PFT and HRCT were obtained clinically and were suggested to be
performed at the study visits; the presence or absence of testing and the results were recorded at each study visit.

Data for this analysis were based on patients enrolled in jSScC from January 2008 to January 2020 who had recorded PFT parameters and an HRCT to determine the sensitivity of PFT detecting ILD. Standard statistics to evaluate the discriminative ability of FVC and DLCO to detect ILD presence/absence, such as sensitivity, specificity or area under receiver operating characteristics curve (AUC), were calculated. The proportion of patients with positive findings in HRCT was compared by means of a logistic regression model. Chi-square or t-test were used to determine differences between characteristics of those with and without HRCT performed (p <0.05 used for significance). To identify clinical characteristics as potential predictors of ILD a univariable logistic regression of the individual clinical measures was performed, followed by a multivariable model using backward selection (p < 0.10) to analyze those variables significant in the univariable model.

Results

Demographics. Of the 150 patients enrolled in the jSScC at the time of data query, 86 (57%) had both CT imaging and an FVC reading from PFT for direct comparison. Among those, 77% (66/86) had diffuse subtype and 80% were female. Mean disease duration was 3.1 years (SD 3.0) and mean age at onset of Raynaud’s phenomenon was 10.1 years (SD 3.9). Seventy-nine (92%) patients were older than 8 years at the assessment of PFT and HRCT (Supplement Table 1). To assess for bias in those with available studies for the test performance of FVC and DLCO, jSSc patients with reported PFT parameters and who underwent an HRCT (n=86) were compared to patients without these examinations (n=64), and were found to be comparable across multiple demographic and clinical characteristics, including disease severity assessment, with the only exception being a higher proportion of pulmonary involvement (59% vs. 25%, p<0.001, respectively; Supplement Table 1). Disease prevalence of ILD, defined as HRCT findings consistent with ILD, was 44% (38 of the 86 with HRCT). Clinical characteristics of the 38 children with ILD on HRCT compared to those 48 without evidence on HRCT via univariate analyses demonstrated a higher mRSS and gastrointestinal involvement to associate with the presence of
ILD on HRCT (p<0.05, Supplementary Table 4a), with multivariable model analysis of these factors supporting a trend towards significance of a higher mRSS and significant association between the presence of gastrointestinal involvement and ILD on HRCT (p = 0.046, Supplementary Table 6).

**Test performance of FVC.** Table 1 presents the association between FVC <80%/≥80% and presence of ILD on HRCT. The discriminative ability (AUC) of FVC as a test to detect ILD was 0.58 (95%CI: 0.48 ; 0.68). The sensitivity and specificity were 40% and 77%, respectively.

**Test performance of DLCO.** DLCO readings were recorded in 71 jSSc patients from the data query and 58 of them had accompanying HRCT readings. Disease prevalence of ILD was 43% (25/58). The AUC of DLCO <80%/≥80% to discriminate between patients with and without ILD on HRCT was 0.73 (95%CI: 0.61 ; 0.85, Table 1). The sensitivity and specificity were 76% and 70%, respectively.

**Test performance of FVC and DLCO.** Both FVC and DLCO were reported in 59 patients. Five of the 26 (19%) that had both parameters, FVC and DLCO, measuring above the threshold of 80% (normal cut off), had an abnormal HRCT (Supplement Table 2). Both FVC and DLCO values were recorded as below 80% for 12 patients, of these 9 (75%) had ILD on HRCT. The discriminative ability of both DLCO and FVC ≥ 80% versus both DLCO and FVC < 80% in relation to HRCT findings was 0.76 (95%CI: 0.61 ; 0.91), with a sensitivity and specificity of 64% and 88% (Supplement Table 3). Patients with conflicting PFT (FVC <80% and DLCO ≥80%, n=5; FVC ≥80% and DLCO <80%, n=16; Supplement Table 2) had about a 50% detection of ILD on HRCT and were excluded from this combination analysis. Patients with DLCO<80% were more likely to show abnormal findings in HRCT irrespective of FVC (Supplement Table 2).

**Receiver-operating curve.** The receiver operating characteristics curves for continuous values of FVC, DLCO, and the combination of FVC and DLCO are shown in Figure 2. The AUC, reflecting the performance of the PFT variables to detect patients with ILD on HRCT, was lower for the FVC (AUC=0.65, 95%CI: 0.53 ; 0.77) compared to the DLCO (AUC=0.80, 95%CI: 0.67 ; 0.92) and the combination of FVC and DLCO (the minimum of FVC and DLCO was selected for combining both tests, in 69% of patients the DLCO was counted because of its lower value compared to FVC; AUC=0.82, 95%CI: 0.69 ; 0.93).

**Alternative FVC and DLCO cut offs.** In addition to the performance of traditional thresholds for healthy children (80%), alternative thresholds of FVC and DLCO of 75%, 85% and 90% were
examined on an exploratory basis. The sensitivity, specificity, PPV, NPV and AUC are reported in Supplementary Tables 5 and 6. The combination of increased sensitivity (58% and 84%) without losing too much specificity (71% and 70%) while gaining the maximum AUC (0.64 and 0.77) is reflected in the 85% cut off for both the FVC and DLCO, respectively. DLCO remains to have superior discernibility over the FVC using the alternative thresholds.

Discussion
This is the first pediatric evaluation of the discriminatory ability of PFT values, FVC and DLCO, to assess ILD in jSSc patients in context with HRCT. The discriminatory properties of the FVC alone using the traditional threshold of 80% was quite poor, with a sensitivity of only 40%, this would have missed the detection of ILD in 60% (23/38) of the patients with groundglass opacities and reticulations on HRCT. The sensitivity of FVC is much lower in the juvenile patients compared to adult SSc patients [7, 15], where the sensitivity is 0.69 using the same FVC < 80% cut off. The specificity of FVC to detect ILD in jSSc compared to adult SSc patients was similar, 0.73 adult SSc [7] and 0.77 jSSc. The limited discrimination of FVC (poor sensitivity, high false negative) may be a particular problem in jSSc since PFT in children can be more difficult to perform than in adults [10-12]. The DLCO is even more difficult to perform in children aged under 8 years old due to lack of cooperation and much effort is required during the testing [11]. Even though some of these limitations were minimized by our sample of patients being mainly comprised of children older than 8 years old (94%), therefore typically obtaining more reliable FVC and DLCO than younger children, there were still notable limitations of the abilities of these tests to detect lung disease. This may pose even more of a discriminatory problem in younger patients, the general jSScC population (n=150) has approximately 25% of the patients enrolled under the age of 8[2], in which only FVC can be reliably measured as a screening tool for ILD. The high rate of false negatives (60%) seems to be unacceptable. Even with maximizing the FVC with alternative thresholds the best sensitivity of 66% obtained at 90% threshold still provides a high rate of false negatives at 35%, which is still problematic for screening purposes in a cohort with potential serious pulmonary involvement.
Applying the DLCO measurement does assist in the detection of ILD, with a reasonable sensitivity and specificity of 76% and 70%, respectively using the standard 80% threshold. Comparable results are also reported in adult SSc [7, 13]. The ability of PFT to detect ILD can be improved when DLCO is combined with FVC (sensitivity and specificity of 64% and 88% respectively). Although the combination of FVC and DLCO provides good discriminatory properties, the caveat, as mentioned, is the 1) limited ability of children to perform the DLCO and 2) the limitation to interpret diagnostic properties of PFT if the two parameters, DLCO and FVC, are contradictory, one is normal and the other is abnormal. The prevalence of ILD in both jSSc and adult SSc is frequent enough that the negative predictive value (NPV) of the clinical screening test should be high enough to ensure that the SSc patients with a negative screening test, FVC and DLCO >80% in this instance, indeed do not have the condition of interest, ILD. The NPV of FVC in jSSc is low at 62%, with a more adequate NPV of the DLCO (79%), consistent with adult DLCO data [7, 15]. Even with similar DLCO NPV values, the adult rheumatology community have found PFTs for screening for ILD in SSc patients alone inadequate, and endorse a baseline HRCT in tandem with PFT given the number of patients with ILD not detected by PFT alone (up to 50% in one study)[9].

In agreement with our adult rheumatology colleagues, our data supports relying on PFT alone for screening for ILD in jSSc is inadequate and would have missed the detection of ILD in almost 2/3 of the sample cohort, supporting the tandem use of HRCT for detection of ILD in children with jSSc.

Additional clinical information, which may assist in identifying those at risk for ILD in jSSc, increasing the positive predictive value, includes the degree of skin thickening assessed by mRSS, and even more so, from the multivariable model is the association with gastrointestinal involvement. An average mRSS of 20 compared to 12 was seen in those with ILD compared to those without in the univariate analysis (p=0.016), which supports a possible relationship between the extent of skin thickening with the presence of ILD. This has been established in adult SSc with diffuse cutaneous patients having higher frequency of ILD, especially in earlier disease when skin score is advancing [16]. Gastrointestinal (GI) involvement remains significant in the multivariable model providing a stronger support for its association of the presence of ILD. Esophageal abnormalities, including dysmotility, low esophageal pressure and contractility, bolus...
clearance abnormalities and larger esophageal diameter (dilated, patulous), have been associated with ILD defined by HRCT findings and abnormal PFT in adult SSc [17]. Although debatable as far as causality of ILD, there is an association between the two with the idea that abnormalities in esophageal function and compromised esophageal integrity allow for stasis of esophageal contents, leading to chronic microaspiration, augmenting ILD [17]. A recent study in jSSc does indeed also support abnormal esophageal findings on upper GI tests (abnormal esophageal peristalsis or bolus clearance) and increased esophageal diameter on HRCT to significantly associate with restrictive lung function, with decreased FVC, FEV1 and VC [18]. Further investigation of adding such clinical characteristics likely influencing ILD, like GI involvement, into the PFT sensitivity and specificity model is warranted once larger number of patients with completed studies are enrolled.

Our study has several limitations. This is an observational clinical study performed across multiple institutions to comprise the international multicenter cohort, therefore PFT and HRCT were collected clinically and not as a requirement to be standardly collected in all patients, reflecting the current standard of care. Eighty-six out of 150 registry patients (57%) had available HRCT to include in the sensitivity and specificity analyses. This may have enriched our population for patients with pulmonary disease. However, the 44% prevalence of pulmonary involvement in our cohort reflects reported prevalence rates in the other published jSSc cohorts (between 36-55%) [2,3], and comparison of jSSc patients in our cohort with and without available HRCT did not reveal any significant demographic, other organ or overall disease severity differences (Supplemental Table 1). Therefore, we do not project that the standardized screening of all consecutive jSSc subjects in our cohort would have resulted in drastically different sensitivity and specificity properties of the PFT in comparison to HRCT findings. An additional general limitation of our study includes the fact that some of the subgroup analyses were based on a limited number of patients, despite of the large cohort of prospectively followed jSSc patients, which must be taken into consideration.

Future directions include confirming our PFT property findings in a validation cohort and evaluating the psychometric properties of sensitivity to change of FVC and ILD in the jSScC cohort longitudinally, as adult SSc studies suggest a decrease of 10% in FVC and 15% in DLCO as poor
prognostic factors and clinically worsening disease [6, 8]. Further study in our cohort once a higher number of subjects are enrolled and screened for ILD could include the analysis of the discriminatory properties of these parameters if the FVC and DLCO thresholds were modified from the 80% cut offs, and the utility of the addition of other clinical characteristics that might predict ILD, such as mRSS and GI involvement.
References


Table 1. Diagnostic test properties of FVC and DLCO as assessment for ILD detection.

<table>
<thead>
<tr>
<th></th>
<th>Forced Vital Capacity</th>
<th>Diffusion Capacity</th>
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<tbody>
<tr>
<td></td>
<td>FVC &lt; 80%</td>
<td>DLCO &lt; 80%</td>
</tr>
<tr>
<td></td>
<td>FVC ≥ 80%</td>
<td>DLCO ≥ 80%</td>
</tr>
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<td>n=86 patients with CT imaging and a FVC reading from PFT</td>
<td></td>
<td>n=58 patients with CT imaging and a DLCO reading from PFT</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ILD on HRCT</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>No ILD on HRCT</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>39.5% (95%CI: 24.0 ; 56.6)</td>
<td>76.0% (95%CI: 54.9 ; 90.6)</td>
</tr>
<tr>
<td>Specificity</td>
<td>77.1% (95%CI: 62.7 ; 88.0)</td>
<td>69.7% (95%CI: 51.3 ; 84.4)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>57.7% (95%CI: 36.9 ; 76.6)</td>
<td>65.5% (95%CI: 45.7 ; 82.1)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>61.7% (95%CI: 48.2 ; 73.9)</td>
<td>79.3% (95%CI: 60.3 ; 92.0)</td>
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<tr>
<td>Area under Curve¶</td>
<td>0.58 (95%CI: 0.48 ; 0.68)</td>
<td>0.73 (95%CI: 0.61 ; 0.85)</td>
</tr>
<tr>
<td>Likelihood ratio (+)</td>
<td>1.72 (95%CI: 0.90 ; 3.3)</td>
<td>2.51 (95%CI: 1.43 ; 4.40)</td>
</tr>
<tr>
<td>Likelihood ratio (-)</td>
<td>0.79 (95%CI: 0.58 ; 1.10)</td>
<td>0.34 (95%CI: 0.17 ; 0.72)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DLCO = Diffusion capacity for carbon monoxide; FVC = Forced vital capacity; HRCT = high resolution computed tomography; ILD = Interstitial lung disease; PFT = pulmonary function tests

¶ Area under Curve estimated for FVC <\= 80% and DLCO <\= 80%
Figure Legends

Figure 1. Interstitial lung disease in a 9 year old girl with systemic sclerosis. Images A through D (cephalad to caudal lungs) demonstrate HRCT findings consistent with ILD, including peripheral groundglass opacities, with distribution in all lobes with hyperdensity in anterior mid (A/B) and lower (C/D) lobes, stacking cystic changes consistent with honeycombing, especially in the anterior upper lobes (A), and subpleural cystic changes in the posterior lower lobes (C/D). Concurrent pulmonary function tests were discordant with the moderate-severe degree of pulmonary involvement seen on CT with an FVC 78% predicted, total lung capacity 96% predicted and DLCO 84% predicted. The patient had been treated with cyclophosphamide, hydroxychloroquine, rituximab, corticosteroids, mycophenolate mofetil, and tocilizumab in order to help stabilize her ILD, underscoring the severity of her condition.

Figure 2. Receiver-operating characteristic curves for % predicted FVC and DLCO demonstrating the discriminative ability as test to detect ILD on HRCT.

[footnote below Figure 2]

(†the minimum of FVC and DLCO was selected for the curve combining both tests; in 69% of patients the DLCO was counted because of its lower value compared to FVC)

FVC = Forced vital capacity; DLCO = Diffusion capacity for carbon monoxide; ILD = Interstitial lung disease; HRCT = high resolution computed tomography