Clinical characteristics and factors associated with disability and impaired quality of life in children with juvenile systemic sclerosis

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Abstract
Objective—To investigate clinical manifestations of juvenile systemic sclerosis (jSSc), including disease characteristics and patient quality of life, through the multinational Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry.

Methods—Subjects with jSSc were prospectively enrolled between 2010 and 2013. Diagnosis of jSSc was determined by the enrolling pediatric rheumatologist, with disease onset required prior to age 18. Collected data included demographics, disease characteristics, medication exposure, and quality of life metrics.

Results—In total, 64 subjects with jSSc were enrolled a median of 3.6 years after disease onset, which occurred at a median age of 10.3 years old. The most common organ manifestations were dermatologic and vascular, followed by musculoskeletal, gastrointestinal, and pulmonary, with 38% of patients having more than four organ systems affected. Patients with jSSc had significantly more disability at enrollment than CARRA registry patients with juvenile idiopathic arthritis, dermatomyositis, or systemic lupus. While physician reported measures correlated most closely with arthritis, skin, and pulmonary manifestations, poor patient-reported measures were associated with gastrointestinal involvement. Over 50 person-years (median duration 1.4 years), there was stability of most organ manifestations with no mortalities or development of new solid organ involvement after enrollment.

Conclusion—In the first multicenter prospective cohort of juvenile SSc patients in North America, disease burden was large: multi-organ manifestations were common, and functional disability was greater than other childhood rheumatic diseases. Gastrointestinal involvement had the greatest impact on quality of life.

“Results from the Childhood Arthritis and Rheumatology Research Alliance Legacy Registry”

Stevens et al.

Juvenile systemic sclerosis (jSSc) is a very rare condition, with a United Kingdom cohort study reporting an incidence rate of 0.27 per million children per year. As in adult onset SSc, jSSc is a multisystem autoimmune disorder primarily characterized by vasculopathy and organ fibrosis. The adult SSc classification criteria has been refined and validated, most recently in 2013 with an emphasis on being inclusive of patients early in the disease course. Although provisional classification criteria for jSSc were developed by a consensus process in 2007, no criteria have been validated for the juvenile condition.

The rarity of the disease in children has resulted in a paucity of data, with larger studies based either upon multi-center, multi-national retrospective reports or upon long-term (multiple decades) retrospective or prospective studies at a single center. The pediatric studies have demonstrated differences between juvenile and adult SSc, including lower mortality rates, and differences in frequency of diffuse versus limited subtypes. However, the 6-15% mortality rate associated with jSSc, indicates the need for a better understanding of risk factors associated with mortality. There is also a need to develop standardized classification and outcome measures for jSSc to work towards identifying optimal treatment strategies.
In 2010, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) established a multicenter prospective observational web-based registry in North America of major pediatric rheumatic diseases, including jSSc.

The objective of this study is to describe disease manifestations of jSSc and how these relate to patient- and physician-reported outcome measures in a cross sectional analysis, with an assessment of disease progression through a longitudinal cohort analysis for a subset of patients with one to two years of follow up.

**Patients and Methods**

**Study Population**

The CARRA registry is a multi-center web-based registry established by pediatric rheumatologists in North America to prospectively capture information about multiple pediatric onset rheumatic diseases.[9] Between 2010 and 2015, 9,579 children were recruited across 65 sites in North America, of which 31 sites enrolled patients with jSSc. Institutional review board approval was obtained at each enrolling site. Subjects and/or a parent/legal guardian were required to provide informed consent.

Subjects were eligible for inclusion in the registry if they had pediatric rheumatic disease onset prior to age 18 and were less than 21 years old at time of enrollment. Diagnosis was determined by a CARRA pediatric rheumatologist.

**Data Collection**

Clinical data were collected from the subjects, guardians, and medical providers using both general and disease-specific standardized case report forms (CRFs) at the time of enrollment and each follow-up visit, with material then entered into a secure web-based registry. Collected information included demographics, physical examination findings, organ manifestations, scleroderma-related auto-antibodies, outcome measures, and medication exposure. Clinical data collected at each visit for subjects with jSSc are listed in Table 2.

For all patients in CARRA, identical questionnaires regarding physical functioning and quality of life were performed with both patient and physician reported outcomes. Patient and/or caregiver reported measures included the Childhood Health Assessment Questionnaire (C-HAQ; where 0=normal and 3=worst)[10, 11], health-related quality of life measure (HRQOL) [12], patient reported global well-being (GWB), and pain scores (range 0-10, where 10=worst pain) or Faces Pain Scale- Revised[13, 14]. Physician based assessments measured included the American College of Rheumatology (ACR) functional class rating[15], which represents levels of functional disability represented by classes I (no disability)- through IV (severe disability), and scaled physician global assessment of disease activity (PGA-DA, range 0-10, where 10=very active). BMI z-scores were calculated based on age and gender normative data by height and weight collected at enrollment.[16] Data were pooled and stored in a secure centralized i2b2 electronic database and de-identified prior to analysis.
**Statistical Analysis**

Statistical Analysis was performed using SPSS software, version 23. Descriptive statistics were computed to summarize each variable, including mean, median, SD, and interquartile range (IQR) for continuous variables or frequencies for categorical variables. Mann-Whitney U and Fisher’s exact tests were utilized for comparisons between physician and patient scored measures and jSSc clinical manifestations. Comparisons between rheumatologic diseases in CARRA, including patient characteristics and quality of life measures, used parametric ANOVA with Tukey HSD (honestly significant difference) for post-hoc pairwise comparisons. Wilcoxon Signed Rank and McNemar’s tests were used for comparison of baseline and follow-up patient data. P values <0.05 were considered significant.

**Results**

**Enrollment and Demographics**

Of the 9,579 patients enrolled in CARRA, 65 children were enrolled from 31 centers with a diagnosis of juvenile systemic sclerosis (jSSc). One subject was excluded from analysis, as multiple diagnoses were listed at the initial visit and jSSc was not listed as a diagnosis on a subsequent visit. Of the 64 children included in analysis, overlap with juvenile dermatomyositis was identified in 3 individuals, and with mixed connective tissue disease in one child. The cohort (Table 1) was primarily female (84%), Caucasian (78%), and identified as non-Hispanic (86%). CARRA enrollment occurred at a median of 3.6 years after disease onset (either Raynaud phenomenon or other symptoms). The median age of onset was 10.3 years old. Median age at first pediatric rheumatology evaluation, which has previously been used as a proxy for diagnosis, was 11.8 years old. Twenty three percent of children had a two year or greater delay between symptoms onset and their first pediatric rheumatology assessment.

**Organ Manifestations**

The most prevalent organ manifestations present at the time of enrollment in the CARRA Registry were dermatologic (93%) and vascular (92%), with Raynaud phenomenon as the most common feature (Table 2). Approximately equal frequencies of pulmonary, gastrointestinal, and musculoskeletal involvement were identified (34–46%), while cardiac and renal manifestations were rare. The presence of scleroderma renal crisis was excluded by the absence of abnormal creatinine in any subject and hypertension alone in one individual. Because jSSc is a multisystem disease, we evaluated the disease burden via the number of organ systems affected. Multiple organs were affected in 93% of subjects, with 38% having four or more organs affected at enrollment.

**Auto-antibodies**—Autoantibody data was available for 63 subjects (see Table 2). Anti-nuclear antibodies (ANA) were reported positive in 84%, anti-Scl70 (anti-topoisomerase I) in 46%, and anti-centromere antibodies (ACA) in six of 40 patients tested. Of the 15 patients who were tested for anti-PM-SCL antibodies, three were positive. Fourteen individuals with a positive ANA had no known extractable nuclear antigen identified. Correlations of scleroderma-specific autoantibodies with clinical features found an association between the presence of digital ulcers with anti-Scl-70 positive status (p=0.035), and presence of...
telangiectasia with ACA (p =0.007). All patients with anti-Scl 70 antibody had vascular involvement.

**Medications**—Reported classes of medications used prior to enrollment in the jSSc CARRA cohort were disease modifying anti-rheumatic drugs (DMARDs) in 87% of subjects, including corticosteroids in 53%, intravenous (IV) immune globulin in 6% and biologics in 4%. DMARDs used prior to enrollment included oral methotrexate (22%), subcutaneous methotrexate (20%), hydroxychloroquine (6%), pulse IV cyclophosphamide (6%), mycophenolate (6%), and sulfasalazine (2%). Medication use at the time of enrollment trended toward greater use of methotrexate (oral 20% and subcutaneous 35%), hydroxychloroquine (28%), and mycophenolate (24%). Corticosteroid administration was commonly reported, with use of systemic corticosteroids reported in 27% prior to enrollment and an additional 20% of patients at enrollment. The frequency of IV pulse corticosteroid use was stable prior to (9%) and at (6%) enrollment. Of the 30 patients who had taken systemic corticosteroids, 25 (83%) had received daily steroid greater than one month during the treatment course. Biologic therapy with etanercept and abatacept were used in one patient each at enrollment.

**Patient-Reported and Physician Measured Outcomes**

Patient/family-based and Physician-based disease metrics at the time of enrollment were analyzed. Patient- and parent-reported outcomes included the Global Well-Being Scale (GWB, “Considering all the ways that your rheumatic condition affects you, rate how you are doing”). The GWB in the jSSc cohort had a median score of 3 (IQR 1-5) with 0 being “Very Well” and 10 being “Very Poor”. Health Related Quality of Life (HRQOL, “How do you rate your health?”) for most was reported as either “Very Good” or “Good” (35% and 44%, respectively), with no individuals reporting “Very Poor.” Using a pain scale specifically asking about “pain related to the rheumatic condition” within the past week, (0=no pain, 10=severe pain), 40 (64%) parents/patients reported some pain, with a median of 1 (IQR 0-4). The median score for the CHAQ was 0.13 (IQR 0-0.63), indicating that most patients were not reporting significant difficulties or limitations.

The physician-scored ACR functional class was class II or greater, indicating some disability, for 36% of individuals at enrollment and 74% at the worst ever function during disease course. The majority of patients did not have reported disability at the time of enrollment, which is reflected in low CHAQ scores. The median Physician Global Assessment of Disease Activity (PGA-DA) score was 2 (IQR 1-3).

**Associations of Specific Disease Manifestations with Quality of Life Measures**

Metrics of disease activity and patient quality of life were analyzed for associations. Patients with more regions of the body affected by skin disease had significantly higher physician global activity (p<0.005) but this was not reflected in functional measures or patient quality of life. The presence of digital ulcers, arthritis, or restrictive lung disease all had significant impact on physician and patient reported measures. In contrast, the most impact on patient reported QoL and physician-reported functional disability occurred in those with gastrointestinal involvement. Conversely, those without gastrointestinal disease had the best
Global Well Being (GWB) scores, while those with gastrointestinal disease had the worst GWB scores (1 vs 5, \( p = 0.01 \)). Similar findings were seen for the pain scale (0 vs 5, \( p < 0.005 \)). There was also a non-significant trend towards higher impact on the CHAQ and HRQOL scores for patients with gastrointestinal disease.

SSc gastrointestinal involvement is multifaceted and is implicated in the processes of malabsorption in SSc, resulting in weight loss, and lower body mass index (BMI), and in children, poor growth. BMI has been recognized as an essential marker of overall well-being, and was included in the proposed jSSc Severity Score.[17] To assess nutritional status, age-specific BMI Z-scores were calculated. In the CARRA jSSc cohort, 14% of the patients had z-scores less than -2, indicating moderate to severe malnutrition (Figure 1).

**Quality of Life and Functional Impact in Comparison to Other Pediatric Rheumatic Diseases**

Quality of life indicators in patients with jSSc were compared to patients with other pediatric rheumatologic conditions, including juvenile idiopathic arthritis (JIA) (n=6525), systemic lupus erythematosus (SLE) (n=995), juvenile dermatomyositis (JDM) (n=629), and localized scleroderma (LS) (n=389). For all groups, enrollment occurred at a mean of 4.5 years after onset (mean ranges 3.4-4.7 years).

Examining quality of life (QoL) measures between groups, GWB and pain reported by jSSc patients/parents were found to be similar to JIA, JDM, SLE, and LS (Figure 2). Functionally, CHAQ scores were not significantly different between jSSc (0.45), JIA (0.38), SLE (0.26), and JDM (0.41). However, when ACR functional scores were examined, children with jSSc were significantly different from their peers with pediatric rheumatic diseases. Patients with jSSc had significantly greater rates of any disability (Class II or higher) reported at enrollment (36%) than SLE (18%, \( p = 0.001 \)), JIA (20%, \( p = 0.004 \)), JDM (21%, \( p = 0.009 \)), and LS (11%, \( p < 0.001 \)). BMI z-scores were significantly lower in jSSc patients compared to all other groups (means -0.13 for jSSc, 0.36 for JIA, 0.71 for SLE, 0.48 for LS, and 0.60 for JDM, \( p < 0.05 \)) (Figure 1). Additionally, the proportion of jSSc with z-scores less than -2 was 14% compared to 1 - 2% in the other conditions, indicated an overall tendency toward poorer nutritional status.

**Longitudinal Assessment of Clinical Outcomes**

Throughout the two year study period, 41 children (64%) had one or more follow up visits recorded with a median follow up of 1.21 years (IQR 0.75-1.96). During the cumulative 50.7 person years of follow-up during the jSSc CARRA study period, there was no mortality reported. There was no interval new development of solid organ manifestations (cardiac, pulmonary, or renal) after enrollment.

To assess for changes in frequency of disease manifestations over time, we performed a subanalysis on a limited number of subjects. Twenty-five subjects had complete clinical data at enrollment and at least one visit one to two years later (median 1.4 years, IQR 1.05-1.88). This subset of patients was similar in demographics (gender, race, ethnicity) to the full patient cohort, although age of disease onset was younger (median 8.9 vs 11.1, \( p = 0.027 \)).
Overall, disease manifestations remained generally stable or improved between enrollment and the 1-2 year follow up period (Figure 3). Longitudinal paired analysis revealed a decreased number of patients with arthritis (from four to one) with an increase in the number of patients with joint contractures from seven to eleven. Trends in disease metrics demonstrated general improvement, with decreased disability by ACR functional class (44% with any disability decreased to 25%) and improved median Physician Global Disease Activity Score from 3 to 2.

When compared to follow-up data one to two years after enrollment, most medication use was stable, with the exception of an increase in use of mycophenolate (58%) and hydroxychloroquine (38%), and no individuals receiving cyclophosphamide.

**Discussion**

This study represents the largest multi-center North American prospective jSSc cohort to date. The only previously published study to prospectively collect clinical data on jSSc patients was limited to a single center[7]. In a limited comparison, the frequencies of organ manifestations over the course of disease represented in this study are similar to the jSSc cohort described by Martini et al in 2006, except that the current study included three patients with juvenile dermatomyositis/scleroderma overlap and one patient with mixed connective tissue disease[4]. Overlap syndrome or MCTD was reported here in four individuals (6%), in contrast to 29-37% of patients in other cohorts [7, 8], identifying potential under-reporting or mis-classification of this subtype in the CARRA jSSc cohort. Data regarding the subtyping of jSSc into diffuse cutaneous and limited cutaneous disease was not collected, limiting our ability to compare this breakdown to prior cohorts.

Significant morbidity was identified within this cohort, with more than two thirds having three or more organ systems affected by the disease. Vascular and dermatologic manifestations were the most common, followed by musculoskeletal, gastrointestinal, and pulmonary manifestations. Renal and cardiac manifestations were rare. Of note, there were no cases of scleroderma renal crisis (SRC) reported in this cohort, despite relatively frequent corticosteroid use. The absence of SRC in our cohort of 64 patients is consistent with the data from the previous multicenter retrospective study [4], in which only 1 of 153 jSSc patients had this manifestation. SRC is reported far more frequently in adult SSc, with corticosteroid use being a known potentiator [18]. This underscores that despite many overlapping features between jSSc and adult SSc, there are also differences.

Overall, the findings in the CARRA jSSc cohort were comparable to previously reported major jSSc cohorts.[4–8] From limited comparison, baseline clinical data are similar to the jSSc cohort described by Martini et al in 2006, except for the inclusion of patients with overlap syndrome or MCTD[4]. Within the brief longitudinal time of the CARRA cohort, there was no mortality. Cardiac manifestations consisted of a single case of pericardial effusion at enrollment, and two cases during follow-up reported as “other”, i.e. not pericardial effusion, arrhythmia, cardiomyopathy, or angina. This is different from the Scalapino jSSc cohort, which also described low frequency of cardiac involvement, but the manifestations were severe and the leading cause of mortality in that cohort [7]. Potentially,
these differences could be related to differences in treatment approaches over the past decade, including more frequent utilization of DMARDs such as mycophenolate; a change seen even between enrollment and follow-up within this cohort.

Patients who reported the worst quality of life had gastrointestinal disease, arthritis, or pulmonary disease, while extent of skin involvement did not appear to have as significant an impact on quality of life. In contrast, poorer physician assessments were associated with skin disease, but not gastrointestinal involvement. The discrepancy between patient and physician assessments deserves more detailed dissection in future studies. Such studies collecting prospective data should consider gastrointestinal specific patient reported outcome measures, especially given the known relationship between GI manifestations and quality of life in adult SSc.\(^{18, 19}\) Data should be collected in conjunction with objective clinical correlates, as in this population the impact of GI disease may be reflected in the significantly lower BMI compared to other pediatric rheumatic diseases.

Patients with jSSc and providers reported impacts on pain and quality of life equally severe to other diseases in the CARRA database. The functional impact of SSc was the most severe of the pediatric rheumatic diseases, with the frequency of some degree of disability at enrollment of jSSc patients being higher compared to pediatric onset SLE, JDM, LS, or JIA. This study identifies the importance of patient centered outcome measures as an adjunct to physician measures in describing the disease burden of jSSc.

Limitations of this study included the lack of available standardized operational procedures designating definitions or methods of assessment of some disease manifestations in the case report forms, including for dysmotility and malabsorption. Case report forms were generally limited to highlight main organ manifestations but were not all inclusive. This included of paucity of certain SSc classification items, such as puffy fingers, fingertip pitting scars, and anti-RNA pol III, which are needed to evaluate the 2013 American College of Rheumatology European League Against Rheumatism classification criteria \(^{2}\). While the CARRA Legacy registry was extensive, this study does represent a multicenter convenience sample of jSSc patients.

The early phase in CARRA Legacy registry development was designed to maximize participation across sites. With the growth of the CARRA network, analysis of data from this initial registry has been utilized to develop a registry designed to collect more refined clinical and serological data. This will allow full evaluation of the performance of the classification criteria. The ongoing funded registry within CARRA is collecting this data alongside patient reported outcomes to provide a multi-dimensional method to better understand how this disease fully affects patients’ lives. For example, it includes an enhanced sensitivity to gastrointestinal disease through collection of defined manifestations and gastrointestinal specific quality of life metrics.

In summary, the CARRA jSSc cohort demonstrated significant morbidity with impacts on quality of life and disability of children with this uncommon disease. While similar in many ways to adult systemic sclerosis, this study also emphasizes the unique nature of systemic
sclerosis in children and the need for further studies utilizing patient and physician outcome measures.

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References


Significance and Innovations

- Significant morbidity is identified in this cohort of juvenile onset SSc patients, with the majority of individuals having multisystem involvement.

- Patients with the worst patient-reported measures of quality of life had GI disease, arthritis, or pulmonary disease, while extent of skin involvement was a significant factor in physician reported measures, but did not have a significant impact on quality of life.

- This study identifies the importance of patient-centered outcome measures as an adjunct to physician measures in describing the disease burden of juvenile onset systemic sclerosis.
Figure 1.
Distribution of BMI z-scores compared between rheumatic disease type of CARRA Registry participants at enrollment. There were a significant portion of jSSc patients with low BMI z-scores compared to other pediatric rheumatology patients. BMI z-scores were calculated based on age and gender normative data by height and weight. jSSc juvenile onset systemic sclerosis; SLE childhood onset systemic lupus erythematosus; JDM juvenile dermatomyositis; JIA juvenile idiopathic arthritis; LS localized scleroderma.
Figure 2.
Distribution of Health Related Quality of Life (HRQoL) responses compared between rheumatic disease type of CARRA Registry patients. jSSc juvenile onset systemic sclerosis; SLE childhood onset systemic lupus erythematosus; JDM juvenile dermatomyositis; JIA juvenile idiopathic arthritis; LS localized scleroderma.
Figure 3.
Comparison of jSSc Organ Manifestations at Enrollment and Follow-up within 1-2 years. Major categories of organ involvement in all patients at enrollment compared to those with enrollment one to two years later. Most manifestations remained generally stable.
Table 1

CARRA jSSc Participant Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54 (84%)</td>
</tr>
<tr>
<td>Race, Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>50 (78%)</td>
</tr>
<tr>
<td>African American</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>55 (86%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Median years (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Disease Onset</td>
</tr>
<tr>
<td>Onset to Diagnosis</td>
</tr>
<tr>
<td>Onset to Enrollment</td>
</tr>
</tbody>
</table>
Table 2
Juvenile SSc Manifestations at Enrollment with Serologic Testing (n=64)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Affected n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
</tr>
<tr>
<td>Skin Thickening/Induration</td>
<td>37 (64%)</td>
</tr>
<tr>
<td>Face</td>
<td>27 (47%)</td>
</tr>
<tr>
<td>Proximal to MCPs</td>
<td>28 (48%)</td>
</tr>
<tr>
<td>Proximal to Elbow</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>36 (62%)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Calciosis</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9%)</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Raynaud Phenomenon</td>
<td>43 (73%)</td>
</tr>
<tr>
<td>Abnormal Nailbed Capillaries</td>
<td>41 (70%)</td>
</tr>
<tr>
<td>Digital Ulceration/Gangrene</td>
<td>27 (46%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Contractures</td>
<td>20 (34%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Myositis</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Tendinopathy</td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Dysmotility</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Documented GERD</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (7%)</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Restrictive Lung Disease</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Decreased DLCO/Hypoxemia</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Radiologic or Histopathologic Fibrosis</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Parenchymal Pulmonary Disease</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3%)</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Renovascular Hypertension</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other Renal</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
Manifestation | Affected n (%)  
---|---  
**Multiple Organs Affected** | 54 (93%)  
Organs Involved  
None | 1 (2%)  
One | 3 (5%)  
Two | 14 (24%)  
Three | 18 (31%)  
Four or More | 22 (38%)  
**Auto-Antibodies** | n=63  
Anti-Nuclear Antibody | n=49/58 (84%)  
Anti-Scl 70 Antibody | n=27/59 (46%)  
Anti-Centromere Antibody | n=6/40 (15%)  
Anti-PM-Scl Antibody | n=3/15  

MCP, metacarpal-phalangeal; GERD, gastro-esophageal reflux disease; DLCO, diffusing capacity of the lungs for carbon monoxide.  
Manifestations with no affected patients reported include: GI stricture, abnormal urinary sediment, elevated creatinine, renal imaging abnormalities, fibrosis on renal biopsy, arrhythmia, cardiomyopathy, or angina.