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# Prediction of Disease Relapse in a Cohort of Juvenile Localized Scleroderma Patients

**K. Kurzinski**[1], **C. K. Zigler**[2,3], and **DR. K. S. Torok**[1]

[1]Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh Scleroderma Center

[2]Department of Physical Medicine and Rehabilitation, School of Medicine, University of Pittsburgh

[3]Human Engineering Research Laboratories, VA Pittsburgh Healthcare System, Pittsburgh, PA

## Abstract

**Background:** Localized scleroderma (LS) is an autoimmune condition of the skin and underlying tissue. Active or recurring disease can lead to cumulative tissue damage, especially in paediatric-onset disease.

**Objectives:** To highlight the rate of relapse of LS activity in a cohort of paediatric patients and to evaluate for potential clinical and laboratory predictors of disease relapse.

**Methods:** Clinical and laboratory data were gathered prospectively. Patients were categorized as experiencing relapse or not, and clinical and laboratory parameters were compared. A logistic regression was fit to predict odds of relapse while controlling for multiple predictors. A subgroup of patients was also evaluated to determine the average time from treatment completion to relapse.

**Results:** Seventy-seven patients were followed for the identified study duration of >2 years and had achieved disease remission, with 35 (48.6%) experiencing LS relapse. Patients who were older at disease onset, ANA positive, and without an extracutaneous manifestation (ECM) were more likely to relapse. All three variables remained significant in the multivariable logistic regression model. Results of the subgroup mirrored the larger sample. The average time between treatment completion and relapse was 21 months.

**Conclusions:** Assessment of LS patients experiencing a relapse of disease activity has shown older age of initial LS onset and ANA positivity to be potential markers for risk of relapse. Patients meeting these parameters may require greater clinical vigilance. The presence of one or more ECM may be protective. Clinicians treating LS patients should provide significant long-term follow-up is warranted to monitor for relapse.

## Introduction

Localized scleroderma (LS) is an autoimmune disease characterized by inflammation of the skin and underlying connective tissue leading to tissue damage, including atrophy,

Corresponding author: Kathryn S. Torok, 4401 Penn Ave., Faculty Pavilion 3000, Pittsburgh, PA 15224 USA, +1(412) 692-5081, kathryn.torok@chp.edu.

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dyspigmentation, and sclerosis. Inflammation, which represents disease activity, is seen clinically as the presence of erythematous, wax-like, or violaceous lesions often with accompanying induration or centralized thickness[1, 2]. Paediatric-onset LS is specifically of concern due to its impact on the growing skeleton and connective tissue of the child, which can lead to significant physical and psychological disability that continues into adulthood[3–6]. Current consensus on the treatment of moderate to severe LS consists of long-term immunomodulation with methotrexate (MTX) and systemic corticosteroids[2, 7]. Treatment studies have shown these medications to significantly reduce the inflammatory burden and to halt the progression of disease activity and subsequent tissue damage[2, 8–10]. However, after initial treatment response (disease remission) and wean of therapy, patients may exhibit a relapse of LS activity. Relapse of disease, especially if left untreated, can result in more disease damage and poorer outcomes for patients. Currently, very little is known about the reasons why relapse occurs or which patients are most at risk.

Generally, treatment decisions are based on physician perception of disease activity, with the initiation of therapy for moderate-severe disease activity, followed by maintenance for a period of inactive disease, and eventual tapering of medications after prolonged inactivity. Markers of increased disease severity have been established and include LS subtype (linear and generalized morphoea), elevation of laboratory markers (CPK, aldolase), presence of extracutaneous manifestations including joint contractures, and presence of anti-histone (AHA), anti-single-stranded DNA (ssDNA), or anti-nuclear (ANA) autoantibodies[5, 11–13]. Other significant extracutaneous manifestations (ECMs) of LS include limb length discrepancy, limb circumference difference, dental issues, uveitis, and arthritis[5, 14, 15]. While these measures may guide initial treatment, they have not been examined with regard to disease relapse incidence. In addition, the standard therapies are associated with frequent and intolerable side effects including nausea, anticipatory vomiting and liver enzyme abnormalities with MTX administration and cushingoid body habitus, irritability and mood swings with the use of systemic corticosteroids[8, 9]. It is therefore of great importance to balance the duration of treatment with the risk of eliciting disease relapse.

This study was designed to describe the rate of relapse in paediatric LS patients within the National Registry for Childhood Onset Scleroderma (NRCOS), to compare the patients experiencing LS relapse to patients who have not experienced relapse to determine clinical and laboratory differences, and to statistically identify potential predictors of LS activity relapse. A more detailed investigation was undertaken with patients who were compliant with their treatment for two years to determine how aggressively patients should be monitored for relapse after appropriately completing treatment.

## Methods

### Participants

Patients were enrolled in the institutional review board-approved National Registry of Childhood Onset Scleroderma (NRCOS). The NRCOS is a combination data registry and specimen repository that was created in 2003 to facilitate research on paediatric onset localized scleroderma (morphoea) and systemic sclerosis. The main aim of the NRCOS is to describe the demographic, clinical, laboratory, and immunogenetic profiles of patients with

localized scleroderma (LS) and systemic sclerosis (SSc), as well as to elucidate the natural history and progression of these diseases. Patients were recruited through specialized rheumatology clinics at the University of Pittsburgh and Children's Hospital of Pittsburgh of UPMC, as well as through outside referrals. Patients included from the NRCOS registry for this relapse study were seen from 2003 to 2013, had a diagnosis of paediatric onset (<18 years of age) localized scleroderma (LS) as defined by the criteria of Laxer and Zulian[16], presented with active disease as their initial visit (as defined below), and followed clinically for at least two years. Patients were treated (by the physician; KT); according to consensus protocols with a standardized regimen of subcutaneous (SC) MTX and oral prednisone[2, 8].

**Variables:** The NRCOS registry contains prospectively gathered demographic, clinical, and patient-centred outcomes data. The following study variables were extracted from the NRCOS registry database.

### Demographic and Clinical Variables

Demographic variables, including sex, race/ethnicity, age at initial diagnosis, and age at initial enrolment visit were assessed. Clinical variables included LS disease subtype and number of affected body sites.

Validated measures of disease activity and severity were prospectively collected at each clinical visit, which included the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) and physician global assessments[1, 17]. The LoSCAT includes the modified Localized Scleroderma Skin Index (mLoSSI) which quantifies cutaneous disease activity[1]. The mLoSSI and the physician global assessment of activity (PGA-A) are the core variables defining disease activity in LS[1]. The mLoSSI includes the sum of three separate scores from the following domains: erythema, skin thickness, and new lesion/lesion extension. There is support for its use with paediatric localized scleroderma patients and it has been found to be responsive to change[18]. The PGA-A is graded on a 100mm analogue scale and includes consideration of the following cutaneous variables: new lesions within the previous month, erythema/violaceous colour at the border of the lesion, and skin thickening/induration at the border of the lesion. Patients with a PGA-A and mLoSSI score > 0 were considered to have active disease. Disease was considered clinically inactive with a PGA-A and mLoSSI score of 0[1, 19]. Patients were followed clinically in the range of every 4 to 12 weeks, with outcome measures collected at every visit. Relapse was defined as the presence of disease activity after obtaining clinical inactive disease, as defined above. Physician documentation of disease state (active/inactive) and denotation of disease relapse at each study visit was obtained.

Extracutaneous manifestations (ECMs) were documented prospectively and longitudinally by the NRCOS primary investigator (KT) at each study visit using a standardized clinical research form. Standardized data collection was performed using a comprehensive listing of ECMs based on a literature review of ECMs encountered in other LS cohorts[5]. ECM data were extracted from NRCOS, reviewed by study team for accuracy, and used to create counts of the total number of ECMs ever experienced by each patient.

Treatment data was extracted to determine if patients were on systemic immunosuppressive treatment at each study visit. If a patient was undergoing systemic therapy, the medication, compliance status, reason for non-compliance and the type and number of medication side effects at each study visit were recorded via a standardized Scleroderma Assessment form.

Characteristics of patients who relapsed were retrospectively compared to characteristics of patients who did not relapse, and included patient demographics, lesion symptoms, activity measures, patient and parent global assessment scores, treatment duration and regimen, and the laboratory parameters Antinuclear Antibody (ANA), Anti-Histone Antibody (AHA), single stranded DNA antibody (ssDNA), Creatine Phosphokinase (CPK), and aldolase. ANA was identified by HEp-2 cells using indirect immunofluorescence at the University of Pittsburgh Immunology laboratory. A titre of 1:80 or higher was considered positive.

**Statistical Analysis of Outcomes—**Demographic characteristics of patients in this cohort were analysed in detail, including the length of time patients were followed by the registry. The number and percentage of patients who experienced at least one relapse were described, and the number of multiple relapses reported, along with the physician-reported reason (or suspected reason) for the relapse.

For categorical variables, comparisons between patients who did and did not relapse were made using chi-squared tests and Fisher exact tests (when $n<5$ for a cell), while independent sample t-tests were used to test mean differences between groups for continuous variables.

A logistic regression was fit to the data to determine statistically significant predictors of relapse. Assumptions and model fit were checked. All analysis was performed using STATA 13 (Statacorp, College Station, TX 2013; alpha = .05).

### Subgroup Analysis

Initial results demonstrated a portion of patients with non-compliance as the cause of relapse. To better determine time from completion of treatment to relapse in patients who were compliant with their regimen, a secondary analysis was conducted with a subgroup of patients who had successfully completed a systemic treatment regimen. Inclusion criteria for this analysis included treatment with systemic medications for at least 2 years and no suspected or confirmed non-compliance throughout treatment duration. Clinical characteristics and laboratory data were compared between patients who relapsed and patients who did not relapse after completing treatment. Time from treatment completion to relapse was calculated.

## Results

### Rate of relapse in this cohort

One hundred and thirty-seven LS patients in the NRCOS were queried for possible inclusion in the study. Seventy-seven patients met inclusion criteria, with 35 patients (48.6%) experiencing at least one LS relapse after initially reaching inactive disease status. Demographic, clinical features and laboratory data are summarized in Table 1. The total group had a female to male ratio 2.3:1, the most common subtypes were linear trunk/limb

(55%), plaque morphoea (circumscribed superficial) (27%) and linear face (16%). The vast majority (87%) of patients meeting inclusion criteria initially underwent systemic therapy consistent with consensus treatment studies including subcutaneous methotrexate and oral prednisone, and were equally present in both relapse and non-relapse groups (Table 2)[2, 8]. Fifteen patients 43% (15/35) were undergoing systemic treatment at the time of their first relapse: 9 with MTX alone (prednisone was already weaned off), 5 with combination (MTX and prednisone) therapy, and one with mycophenolate mofetil.

Suspected reasons for initial relapses are listed in Table 1. The most frequent reasons were suspected non-compliance of the patient to his or her prescribed treatment regimen and relapse after completing a standard therapy regimen. To note, rates of non-compliance were similar between the relapse and non-relapse group, (11/35, 31% vs. 7/42, 17%, p-value = 0.13). Non-compliance was only attributed to medication side-effects in two patients, both secondary to methotrexate, with one patient experiencing nausea and another with hair thinning. In most patients, non-compliance was attributed to the patient, in his or her own words, being ‘tired of taking the medications’. Of the 35 patients who relapsed, almost a third (31%) relapsed more than once (n = 11). For patients who relapsed multiple times, the median number (IQR) of relapses was 2 (2, 2.5). Of the patients who relapsed more than once, the reasons for their multiple relapses were mostly attributed to suspected medication non-compliance (35% of multiple relapses).

## Comparison of clinical and laboratory characteristics of relapse and non-relapse patients

Patients who experienced relapse were significantly older at disease onset (10 vs 7 years old), more likely to be ANA positive (60% vs 24%), and less likely to have at least one ECM (28% vs 55%) when compared to patients who did not relapse (Table 2). Gender, LS subtype, medication compliance, time from onset to diagnosis, and follow-up duration were similar between groups (Table 2).

## Logistic regression to determine statistically significant predictors of relapse

A logistic regression model predicting relapse status by age of onset, ANA positivity, and presence of ECMs was fit to the data. Sixty-three patients with complete data were included in the final model. The model exhibited goodness-of-fit, Hosmer-Lemeshow $\chi^2$ (8) = 9.24, $p$ = 0.322, and there was no evidence of multicollinearity. All other assumptions were met. Together, the three variables significantly predicted relapse status, Wald’s test $\chi^2$ (3) = 13.32, $p < 0.01$. The odds of relapse in patients with paediatric LS increased by 23% for every year older at symptom onset (SE=1.23, 95% CI [1.04–1.46]), while ANA positivity increased the odds of relapse by a factor of 4.8 (SE=3.13, 95% CI [1.37–17.2]). Interestingly, the odds of relapse was 80% lower for the group that had at least one ECM when compared to the odds of patients that had no ECMs (SE=0.14, 95% CI [0.06–0.75]). Together, the three variables predicted relapse well, with an AUC of 0.82 (95% CI [0.71, 0.93]).

## Subgroup Analysis

Twenty-seven patients met criteria for inclusion into subgroup analysis (35% of the larger sample), which was completion of recommended course of systemic therapy for at least 2

years. Within this cohort, 11 patients (40.7%) experienced relapse following treatment, which was a slightly lower but similar rate of relapse than in the larger cohort. For the patients who relapsed, the average time between the completion of a therapy regimen and the onset of relapse was 21.1 months, but this varied widely (range 1 month – 52 months). As in the larger cohort, patients who experienced relapse were significantly older at disease onset than the patients who did not relapse, $p < 0.01$ (Table 3). There was not a statistically significant difference in treatment duration between the relapse and non-relapse patients who completed systemic treatment, however, relapse patients were on average treated six months less than the non-relapse patients (Table 3). All other clinical and laboratory comparisons between groups, including ANA positivity, sex, and disease subtype, were not statistically significant in patients who had completed treatment, though results are limited by smaller numbers (Table 3).

## Discussion

There is a clinical need to determine demographic, clinical, and serologic variables associated with and predictive of disease relapse in localized scleroderma to assist in counselling families regarding prognosis and physician management of systemic therapy. We specifically only included patients from our cohort for this study who had met criteria for active disease at baseline visit, obtained inactive disease at subsequent study visits, and were followed for a minimum of 24 months. Assessment of paediatric onset localized scleroderma (LS) patients experiencing a relapse of disease activity meeting these criteria has shown older age of initial LS onset and ANA positivity to be potential markers for risk of relapse. These circumstances may warrant greater clinician vigilance of patient disease state throughout treatment and following treatment completion.

Relapse association with older age of LS onset has also been seen in another sizable cohort of paediatric onset LS patients[20]. One of the impressions of the authors to explain this finding was poor compliance among teenagers. However, in the subanalysis of those in our cohort who were fully compliant with therapy and completed their recommended treatment course, the older age of onset was still shown to be associated with a higher incidence of relapse. An older age at disease onset in a paediatric patient may signify a more robust immune involvement in the disease course, increasing the likelihood of LS relapse. ANA positivity may more specifically indicate a higher level of immune system autoreactivity, thus indicating a greater propensity LS relapse in our total sample. In the subgroup analysis, it is important to note that 55% of patients who relapsed after completing treatment were ANA positive (compared to 27% of patients who did not relapse after treatment). Although this did not reach statistical significance, this test was likely not sufficiently powered due to the smaller sample size. Not consistent with this theory of higher immune reactivity is the equal distribution among relapse and non-relapse groups of the other auto-antibodies commonly observed in LS, anti-histone Ab and anti-ssDNA Ab, in both the overall and subgroup analyses. Our group is currently evaluating peripheral blood markers, such as cytokines and chemokine signatures, as another avenue to evaluate the general immune status between the relapse and non-relapse groups.

Surprisingly, the presence of joint contractures (deep tissue involvement) and other ECMs do not seem to represent an inherent risk of relapse after achieving disease inactivity, with analyses showing that the presence of an ECM indicate that the patient would be *less* likely to relapse. This could potentially be attributed to physicians treating patients who experience these more aggressively, especially since ECMs are considered validated indicators of severity. A post-hoc analysis indicated that patients with at least one ECM were treated on average about 8.4 months longer (mean 3.9 ± 2.4 years) than patients without ECMs (mean 3.2 ± 1.9 years), although the difference was not significant, $t(73) = 1.43$, $p = 0.16$.

An additional contribution might be earlier treatment with systemic therapy if a musculoskeletal (MSK) ECM, such as joint limitation, is present. The LS subjects in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry cohort with MSK ECMs (n = 89 out of 386) were referred more rapidly to paediatric rheumatologists and started treatment with systemic therapy earlier compared to those LS patients without MSK ECMs[11]. A recent publication of a large longitudinal European cohort (n=133) also supports lower relapse rates in those starting systemic therapy earlier in their course[21]. The most common ECM in our cohort is musculoskeletal, including deep involvement of the facia and muscle, leading to joint contractures, fasciitis and myositis. The elevated muscle enzymes, CPK and aldolase, in approximately 30% of these subjects further supports this observation. Interestingly, the proportion of those with elevated muscle enzymes are quite evenly distributed between the patients who relapsed and those who have not, again, not favouring relapse. We did observe more joint contractures clinically among the non-relapse group compared to relapse (35% vs 28%). Again, this possibly supports the theory that these patients are treated more aggressively or referred for therapy earlier, especially since musculoskeletal ECMs are physically obvious and in general considered a reason to treat more aggressively with systemic medication[2, 22].

A clinical variable that was not associated with relapse in this cohort was subset of LS disease. This was in contrast other cohort studies; both Mertens et al and Mirsky et al found the linear limb subtype was related to increased risk for relapse[20, 23]. All three cohorts (including ours) were representative of the typical distribution of paediatric-onset LS, with the most common subtypes being linear limb, plaque (circumscribed superficial), and linear face, therefore the subtype distribution of this cohort should not have affected our observations[20, 23]. The subanalysis of patients who were compliant and completed at least 2 years of therapy did show that those with deeper tissue involvement (i.e. linear limb and deep morphoea) were the most common subtypes to flare (Table 3), although statistical comparisons could not be performed due to very small sample sizes. Again, this may reflect the tendency of clinicians to treat those with linear limb disease, especially with initial joint contractures or other MSK ECMs, more aggressively. Further investigation into treatment dosage and regimen may help to confirm these trends, and provide more tailored and efficacious therapies for patients with and without ECMs, and further aid in the prevention of relapse.

Overall, patients relapsed around 21 months after treatment was completed, with 68% of relapse occurring between 5 months and 37 months. This is similar to the time frame reported by Mertens *et al*, with time from disease remission to relapse averaging 26 months

[23]. Additionally, a relatively high relapse rate was seen after completion of a full course of treatment with systemic medications (11 out of 27, 40.7%). Other studies have shown varied rates of relapse after the discontinuation of methotrexate and systemic corticosteroid therapy, with percentages of 12.5%[23], 27 %[10], 29%[20], and 44%[24]. Additionally, rates of relapse in a dermatology cohort including both paediatric and adult LS patients treated with alternative methods (UVA1 phototherapy) was similar to ours (46%)[25]. Variability among treatment protocols and study design may contribute to the difference in observed rates of relapse after therapy discontinuation. However, the significant burden of relapse among all cohorts emphasizes the importance of regular follow-up visits, even after a prolonged period of disease inactivity.

There are a few limitations of this study that deserve discussion. First, the study was limited by the relatively small sample of patients who have completed the prescribed therapy regimen. However, the overall group sample size is similar to prior studies regarding relapse in LS, which is a rare disease[23]. Future studies should confirm these findings and specifically explore treatment dosage, regimen, and duration prospectively in a larger group of patients with a longer duration of follow up. Additionally, it is possible that sampling bias may have limited data to those who have more severe disease at baseline, as they are likely to require longer-term follow-up.

This study is innovative in that it utilizes prospectively collected and standardized clinical and laboratory information to assess the occurrence of relapse in a large cohort of paediatric LS patients. Inclusion criteria were rigorous and included patients who entered the study with active disease, subsequently achieved inactive disease status, and were followed for a minimum of 24 months. These results can be used to identify patients who might be more likely to experience disease relapse and require longer or more aggressive treatment with systemic medications. This study also highlights that patient non-compliance (suspected or determined) is likely a prominent issue in patient relapse. Although methotrexate and corticosteroids are effective in treating LS, they are limited by their tolerability. Further investigation into reasons for patient non-compliance, qualitative experiences of negative side effects from systemic treatment, and the identification of potential alternative therapies is needed.

For clinicians managing paediatric LS patients, we recommend following patients for at least 3 years after disease activity is halted, as disease relapse can occur after an extended period of inactivity. Special attention should be paid to patients who are older at the onset of disease and are ANA positive, and future studies should explore the relationship between ECMs, treatment duration, and relapse.

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**What's already known about this topic?**

- Localized scleroderma is marked by periods of disease inflammation (activity) that can yield cutaneous and connective tissue damage that can lead to significant physical and psychological disability.
- Some paediatric patients with localized scleroderma experience a relapse of disease activity after initially achieving disease remission.

**What does this study add?**

- This study highlights the high rate of relapse (nearly 50%) in a cohort of paediatric patients with LS. A positive anti-nuclear antibody and older age at onset were associated with relapse.
- Medication non-compliance with methotrexate and corticosteroids, the cornerstone treatment in LS, can potentially contribute to relapse. New or alternative therapies may be better tolerated and increase treatment compliance.
- General clinician awareness of the high rate of recurrence in LS will help shift the general approach to this condition as a chronic autoimmune condition, recognizing recurrence and reinitiating treatment more promptly.

**Table 1.**

Characteristics of 77 paediatric onset LS patients who were followed clinically for 2 years or more, grouped by those that had a relapse of disease and those that did not

| **Characteristics** | **Total (n=77)** | **Relapse (n=35)** | **No Relapse (n=42)** | **p-value**[1] |
|---|---|---|---|---|
| Gender | n (%) | n (%) | n (%) | |
| Female | 54 (70) | 26 (74) | 28 (62) | 0.23 |
| LS Subtype | | | | |
| Circumscribed Superficial | 21 (27) | 10 (29) | 11 (26) | 1 |
| Circumscribed Deep | 8 (10) | 4 (11) | 4 (10) | 1 |
| Generalized Morphea | 10 (13) | 6 (17) | 4 (10) | 0.5 |
| Linear Trunk/Limb | 42 (55) | 20 (57) | 22 (52) | 0.81 |
| Linear Face | 12 (16) | 3 (9) | 9 (21) | 0.21 |
| Mixed Morphea | 12 (16) | 6 (17) | 6 (14) | 0.76 |
| Pansclerotic Morphea | 2 (2.6) | --- | 2 (4.5) | --- |
| Eosinophilic Fasciitis | 1 (1.3) | --- | 1 (2.4) | --- |
| Laboratory Evaluation[*] | | | | |
| **ANA Positive**[‡] | **26/63 (41)** | **18/30 (60)** | **8/33 (24)** | **<0.01** |
| ssDNA Positive | 31/71 (44) | 13/32 (41) | 18/39 (46) | 0.81 |
| AHA Positive | 26/70 (37) | 9/31 (29) | 17/39 (44) | 0.23 |
| CPK Elevated | 18/71 (25) | 10/34 (29) | 8/37 (22) | 0.59 |
| Aldolase Elevated | 22/66 (33) | 13/32 (41) | 9/34 (27) | 0.21 |
| Extracutaneous Manifestations | | | | |
| **At least one ECM** | **33 (43)** | **10 (28)** | **23 (55)** | **0.02** |
| Joint Contractures | 23 (30) | 8 (23) | 15 (35) | 0.22 |
| Arthritis | 3 (3.9) | 2 (5.7) | 1 (2.4) | 0.59 |
| Dental | 4 (5.2) | --- | 4 (9.5) | --- |
| Uveitis | 1 (1.2) | --- | 1 (2.4) | --- |
| Limb length discrepancy | 5 (6.5) | 1 (2.9) | 4 (9.5) | 0.37 |
| Limb circumference difference | 14 (18) | 6 (17) | 8 (19) | **0.047** |
| Medication | | | | |
| On MTX and CS regimen[¥] | 67 (87) | 28 (80) | 39 (93) | 0.09 |
| Compliance with medication | 18 (23) | 11 (31) | 7 (17) | 0.13 |
| | | mean (SD) | mean (SD) | p-value |
| **Age Onset (years)** | | **10.0 (3.9)** | **6.7 (3.7)** | **<0.001** |
| Time Onset to Diagnosis (mos) | | 13.8 (18.5) | 22.4 (31.4) | 0.16 |
| Follow-up Duration (years) | | 4.3 (2.0) | 4.9 (2.8) | 0.34 |

[1] P-values were obtained using Chi-squared tests for categorical variables and Fisher exact tests when n<5 for a cell. Independent sample t-tests were used for continuous variables. Comparisons were made between relapse and non-relapse groups.

[*] Laboratory parameters not obtained for all patients so denominators are provided.

ANA (antinuclear antibody), ssDNA (single stranded DNA antibody), AHA (antihistone antibody), CPK (creatine phosphokinase)

¥Patients were routinely treated according to consensus protocols with a standardized regimen of subcutaneous (SC) MTX at 1 mg/kg/week (maximum 25mg/week) and oral prednisone 2mg/kg/day (maximum 60mg/day). MTX SC was continued for 24 months and then switched to oral administration to complete 36 months of therapy. Prednisone was tapered and kept at 0.25mg/kg/day for 12 months (Ref 2, 8)

‡The ANA titer and pattern was varied among patients in both relapse and nonrelapse groups, range 1:80 to 1:640

**Table 2.**

Physician-determined reasons for initial disease relapse after a period of disease inactivity in 35 pediatric localized scleroderma patients

| Reason for relapse based on physician reports | n (%) |
|---|---|
| Suspected Non-Compliance with Medication[1] | 11 (31) |
| Completed Therapy, Off Medication in Remission | 11 (31) |
| Breakthrough on Systemic Treatment[*] | 5 (14) |
| Undergoing Medication Taper | 4 (11) |
| Medication Withdrawn due to Toxicity[¥] | 2 (6) |
| Undetermined | 2 (6) |

[1] The majority of patients with suspected noncompliance were noncompliant with methotrexate monotherapy (9/11).

[*] 7 while on methotrexate monotherapy and 7 while on methotrexate plus oral prednisone.

[¥] Two patients developed elevated liver function tests while undergoing treatment with MTX requiring withdraw of therapy.

**Table 3.**

Comparison between relapse and non-relapse patients in a subgroup of 27 paediatric LS patients who completed the recommended course of systemic therapy (>2 years)

| **Characteristics** | **Relapse (n=11)** | **No Relapse (n=16)** | |
|---|---|---|---|
| Gender | *n (%)* | *n (%)* | *p-value*[2] |
| Female | 8 (73) | 11 (69) | 1.00 |
| LS Subtype | | | |
| Circumscribed Superficial | 1 | 5 | |
| Circumscribed Deep | 3 | 1 | |
| Generalized Morphea | 0 | 3 | |
| Linear Trunk/Limb | 6 | 0 | |
| Linear Face | 0 | 4 | |
| Mixed Morphea | 1 | 3 | |
| Pansclerotic Morphea | … | … | |
| Eosinophilic Fasciitis | … | … | |
| Laboratory Evaluation* | | | |
| ANA Positive | 6 (55) | 4 (27) | 0.23 |
| ssDNA Positive | 5 (46) | 5 (33) | 0.69 |
| AHA Positive | 4 (36) | 8 (57) | 0.43 |
| CPK Elevated | 4 (36) | 5 (36) | 1.00 |
| Aldolase Elevated | 5 (45) | 2 (15) | 0.18 |
| Extracutaneous Manifestations | | | |
| At least one ECM | 4 (36) | 8 (50) | 0.70 |
| | Relapse *mean (SD)* | No Relapse *mean (SD)* | *p-value* |
| **Age Onset (years)** | **11.34 (3.53)** | **7.14 (3.51)** | **< 0.01** |
| Treatment Duration (mos) | 38.92 (15.67) | 44.99 (13.28) | 0.29 |
| Follow-up Duration (years) | 5.05 (1.89) | 5.72 (1.59) | 0.99 |

[2]P-values were obtained using Chi-squared tests for categorical variables and Fisher exact tests when n<5 for a cell. Independent sample t-tests were used for continuous variables. P-values not provided for subtypes, as sample sizes were extremely low.

*Laboratory parameters not obtained for all patients so denominators are provided

ANA (antinuclear antibody), ssDNA (single stranded DNA antibody), AHA (antihistone antibody), CPK (creatine phosphokinase)