RETRACTED: Pain predicts poorer health-related quality of life in childhood-onset systemic lupus erythematosus: a cohort study

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Abstract
Objectives: To investigate the predictive value of pain on health-related quality of life (HRQoL) among patients with childhood-onset systemic lupus erythematosus (cSLE), as increased adverse psychosocial events are reported in patients with cSLE, but the predictive impact of psychological events on HRQoL remains unclear.
Methods: This cohort study recruited patients with cSLE from the Cincinnati Children’s Hospital Medical Centre rheumatology clinic. Data regarding pain due to lupus in past week, and HRQoL, were collected during a baseline and 6-month follow-up visit.
Results: Out of 65 enrolled patients, 50 remained for follow-up analyses. At 6-month follow-up, pain was associated with significantly lower Paediatric QoL Inventory (PedsQL) Generic Core scale (GC) scores and PedsQL-Rheumatology Module (RM) scores versus no pain. Using a
general linear model, pain symptoms were associated with decreased HRQoL (predicted PedsQL-GC, $\beta = -13.36$; and PedsQL-RM, $\beta = -12.72$), adjusting for age, sex, British Isles Lupus Assessment Group disease activity index and physician global assessment of disease activity.

**Conclusion:** Further research is needed to clarify the predictive value of pain, and evaluate the potential use of pain measures as indicators for appropriate psychosocial interventions in patients with cSLE.

**Keywords**
Childhood-onset Systemic Lupus Erythematosus, cohort study, health-related quality of life, pain

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**Introduction**

Childhood-onset systemic lupus erythematosus (cSLE) is a challenging disease with widely varying clinical manifestations. The annual incidence of cSLE is estimated to be 2.2 per 100,000 of the US paediatric population,¹ and the prognosis for patients with cSLE is worse than for those with adult-onset SLE.² The clinical course of cSLE is complex and is associated with impaired activities and decreased health-related (HR) quality of life (QoL).³,⁴ In addition, a multi-centre cohort study revealed that obese patients with cSLE tended to have a poorer HRQoL than patients of normal weight.⁵

In a previous cross-sectional study by the present authors, the psychosocial symptoms of patients with cSLE, such as pain, anxiety and depression, were shown to be associated with HRQoL score.⁶ Although pain symptoms are prevalent during the clinical course of cSLE, it remains unclear whether patients with cSLE who experience pain are more inclined to have a poor HRQoL.

The aim of the present cohort study was to evaluate the predictive value of lupus-associated pain on HRQoL, and to gain more insight into risk factors that may predict the need for proactive intervention in patients with cSLE.

**Patients and methods**

**Study population and design**

In this observational cohort study, children and adolescents with cSLE were sequentially recruited from the Cincinnati Children’s Hospital Medical Centre rheumatology clinic between September 2014 and September 2015. Inclusion criteria comprised patients aged between 8 and 20 years and cSLE diagnosis before the age of 18 years, based on the revised American College of Rheumatology Classification Criteria for SLE.⁷ Patients with cSLE comorbidities, and/or chronic diseases, with known effects on HRQoL were excluded.

The study was explained to each participant and legal proxy prior to study participation. Written informed consent and assent were obtained from all patients, and from legal proxies for patients <18 years of age. The study was approved by the institutional review board at Cincinnati Children’s Hospital Medical Centre and was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Data were collected at a baseline visit and at a follow-up visit 6 months later, and associations between pain scores at
baseline and HRQoL scores at the 6-month follow-up visit were analysed.

**Pain and HRQoL measures**

A pain visual analogue scale (VAS) with a score range of 1–10 (where 0 = no pain, and 10 = very severe pain) was used to measure pain intensity experienced in the previous week. The respondent was asked to place a line perpendicular to the VAS line at the point that represented their pain intensity. The score was then determined using a ruler to measure the distance on a 10-cm line between the ‘no pain’ anchor and the patient’s mark, providing a range of scores from 0–10. A pain VAS score >3 was taken to represent clinically meaningful pain symptoms.6

Patient HRQoL was measured using the Paediatric QoL Inventory Generic Core scale 4.0 (PedsQL-GC), a self-report questionnaire including information on physical, emotional, social and school function,8 and the Paediatric QoL Inventory 3.0 Rheumatology Module (PedsQL-RM) questionnaire,9 which highlights domains relevant to children with rheumatic diseases such as pain and hurt, daily activities, treatment, worry and communication. Details and internal reliability of the questionnaires have been described previously.6 Briefly, PedsQL-GC comprises 23 items (score range, 0–92) and PedsQL-RM comprises 22 items (score range, 0–88), with a 5-point scale for each item (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = almost always). Higher scores represent better HRQoL.

**Disease activity and damage measures**

The Systemic Lupus Erythematosus Disease Activity index (SLEDAI; score range 0–105, where 0 = inactive disease),10 the British Isles Lupus Assessment Group (BILAG) disease activity index (measuring disease activity in general, and mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculitis, haematology and renal aspects, with alphabetical scores of A = 12, B = 8, C = 1, D = 0, E = 0; where 0 = inactive disease),11 and physician global assessment of disease activity (MD global; range, 0–10) were used to assess disease activity. Both SLEDAI and MD global have been validated for use in patients with cSLE, and the BILAG was added because it contains items that address subjective symptoms that cannot be objectively measured, including, but not limited to, fatigue, arthralgias and myalgias.12 Disease damage was evaluated using Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) scores.13,14

**Data collection**

Patients completed the self-report questionnaires covering pain, sleep, fatigue, pain coping, pain catastrophizing, mood, anxiety, disease activity, disease damage and HRQoL. The HRQoL questionnaires were validated as previously described.6 Data relating to patient demographics (age, sex, race and ethnicity) were collected from medical records.

**Statistical analyses**

Statistical analyses were conducted using SPSS software, version 19.0 (IBM, Inc., Armonk, NY, USA). Numerical variables are presented as median and inter-quartile range (IQR). Differences in age, SLEDAI score, BILAG score, MD global and SLICC/ACR DI score between patients with or without pain were analysed by Mann–Whitney U-test. Differences between patients with or without pain in terms of sex and ethnicity distributions were analysed...
using Fisher’s exact test, and in terms of race and insurance types was estimated using $\chi^2$-test. Differences in PedsQL-GC and PedsQL-RM between baseline and 6-month visits were analysed using Wilcoxon signed-rank test. Differences in PedsQL-GC and PedsQL-RM between patients with or without pain were analysed by Mann–Whitney $U$-test. Finally, the effects of pain were analysed using a general linear model for PedsQL-GC and PedsQL-RM, with adjustments for age, sex, BILAG score and MD global. All analyses were two-tailed, and a $P$ value <0.05 was considered to be statistically significant.

**Results**

A total of 65 patients with cSLE were initially included, and of these, 15 patients (23%) were lost to follow-up. Distributions of age, sex, race, ethnicity and insurance type were similar between patients with cSLE with or without pain symptoms ($P >0.05$; Table 1). Baseline median BILAG score was significantly higher for patients with cSLE and pain (6.0) compared with patients without pain (2.0; $P <0.001$; Table 2). Baseline MD global score was 86% higher in patients with cSLE and pain symptoms than in patients without pain ($P <0.05$; Table 2). Patients in the two pain groups had similar baseline SLICC/ACR DI and SLEDAI scores (Table 2).

Regardless of pain symptoms, median HRQoL scores increased during the 6-month follow-up period among the 50 patients who were assessed at the follow-up visit. Median PedsQL-GC score increased from 73 at baseline to 81 at the 6-month follow-up visit ($P <0.05$, Figure 1), with score changes in each patient ranging from −25.31 to 27.50. A total of 64% (32/50) of patients experienced an increase in PedsQL-GC Scale score during the 6-month follow-up. The median PedsQL-RM

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**Table 1.** Distribution of baseline demographic characteristics in 65 patients with childhood-onset systemic lupus erythematosus (cSLE) with or without symptomatic pain

| Demographic     | Symptomatic pain | Statistical significance |
|-----------------|------------------|-------------------------|
|                 | No ($n = 36$)    | Yes ($n = 29$)          |                         |
| Age, years      | 16.0 (15.0, 18.0)| 16.0 (14.0, 18.5)       | NS*                     |
| Sex             |                  |                         |                         |
| Male            | 8 (22.2)         | 3 (10.3)                | NS**                    |
| Female          | 28 (77.8)        | 26 (89.7)               |                         |
| Race            |                  |                         | NS***                   |
| Black           | 15 (41.7)        | 12 (41.4)               |                         |
| White           | 19 (52.8)        | 14 (48.3)               |                         |
| Asian           | 2 (5.6)          | 1 (3.4)                 |                         |
| Other           | 0                | 2 (6.9)                 |                         |
| Ethnicity       |                  |                         | NS**                    |
| Hispanic        | 1 (2.8)          | 3 (10.3)                |                         |
| Non-Hispanic    | 35 (97.2)        | 26 (89.7)               |                         |
| Insurance ($n = 57$) |          |                         | NS***                   |
| Public          | 13 (38.2)        | 10 (43.5)               |                         |
| Private         | 21 (61.8)        | 13 (56.5)               |                         |

Data presented as median (interquartile range) or $n$ (%) patient prevalence.

NS, no statistically significant between-group differences ($P >0.05$; *Mann–Whitney $U$-test, **Fisher’s exact test, ***$\chi^2$-test).
among 50 patients increased from 77 at baseline to 81 at the 6-month follow-up ($P < 0.05$, Figure 1), with score changes in each patient ranging from –28.70 to 37.80. A total of 74% (37/50) of patients experienced an increase in PedsQL-RM during the 6-month follow-up.

In patients categorized according to presence or absence of pain, median PedsQL-GC at the 6-month follow-up visit was 82.3 among patients without baseline pain (VAS ≤ 3; $n = 27$) compared with 68.7 among patients with baseline pain (VAS > 3; $n = 23$; $P < 0.05$; Figure 2). Median PedsQL-RM score at the 6-month follow-up visit was significantly higher in patients without baseline pain than patients with baseline pain (84.0 versus 70.4, respectively; $P < 0.05$, Figure 2).

Among patients without pain, median PedsQL-GC was 80.4 at baseline and 82.3 at the 6-month follow-up visit ($P = 0.43$) and median PedsQL-RM was 83.6 at baseline and 84.0 at the follow-up visit ($P = 0.63$). Among patients with baseline pain, median PedsQL-GC significantly increased from 66.1 to 68.7 at the follow-up visit ($P = 0.02$) and median PedsQL-RM significantly increased from 61.5 to 70.4 at the follow-up visit ($P < 0.01$).

Using a general linear model, symptomatic pain was found to have a significant association with reduced PedsQL-GC Scale score, with a correlation coefficient of –13.36 (Table 3, $P < 0.05$). Pain also

Table 2. Distribution of baseline systemic lupus erythematosus (SLE) characteristics in patients with childhood-onset SLE with or without symptomatic pain

| SLE characteristic       | No ($n = 36$) | Yes ($n = 29$) | Statistical significance* |
|-------------------------|--------------|---------------|---------------------------|
| SLEDAI score            | 4.0 (2.0, 8.0) | 4.0 (2.0, 10.0) | NS                        |
| BILAG score             | 2.0 (1.0, 5.0) | 6.0 (4.0, 11.0) | $P < 0.001$               |
| MD global               | 1.0 (0.0, 1.0) | 2.0 (1.0, 4.0)  | $P = 0.007$               |
| SLICC/ACR DI score      | 0.0 (0.0, 2.0) | 0.0 (0.0, 1.0)  | NS                        |

Data presented as median (interquartile range).

SLEDAI, Systemic Lupus Erythematosus Disease Activity index; BILAG, British Isles Lupus Assessment Group disease activity index; MD global, physician global assessment of disease activity; SLICC/ACR DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

*Mann–Whitney U-test.

NS, no statistically significant between group differences ($P > 0.05$).
had an inverse association with PedsQL-RM, with a correlation coefficient –12.72, adjusting for age, sex, BILAG score and MD global score (Table 3, \( P < 0.05 \)).

**Discussion**

In the present cohort study, a statistically significant temporal association was observed between clinical pain symptoms and HRQoL among patients with cSLE. Occurrence of pain symptoms predicted a future 13.36-point reduction in PedsQL-RM scores and a 12.72-point reduction in PedsQL-GC scores. PedsQL-GC and PedsQL-RM are two tools used to measure HRQoL: PedsQL-GC is a generic paediatric measure of HRQoL that is combined with PedsQL-RM, with PedsQL-GC being a relatively brief and easily administered tool, and PedsQL-RM being more sensitive to clinical change having both concurrent and construct validity.\(^{15}\) Peds-GC is more widely used in clinical settings for monitoring changes of HRQoL over time due to its ease of application. PedsQL-RM contains psychometric parameters more relevant to cSLE, and is a useful method of assessing therapeutic effects in observational and clinical trials. Thus, both were used to investigate whether the existence of clinical pain might act as a predictor for reduced HRQoL.

In the present study, patients with cSLE experienced lower HRQoL scores, and pain symptoms were prevalent. As previously reported, cSLE is associated with reduced QoL for patients, and both disease activity and disease-related damage affected HRQoL, which was reflected by the PedsQL-RM.\(^{16}\) The prevalence rate of pain among cSLE patients is reported to be lower than in patients with adult-onset SLE.\(^ {17} \) In the present study, pain predicted a poorer HRQoL among patients with cSLE, and the negative impact of pain on HRQoL was consistent with a previous report by the present authors.\(^ {6} \) Patients with adult-onset SLE are also reported to present with a significant association between pain symptoms and reduced HRQoL scores,\(^ {18} \) and psychosocial pain management strategies have been recommended for children with SLE, in order to achieve a better HRQoL.\(^ {19} \) Thus, indices reflecting the severity of pain may supply useful information to healthcare providers for the identification of appropriate psychosocial interventions.
The results of the present study are limited by the relatively small sample size and relatively high proportion of patients lost to follow-up, thus further studies are required to address these issues. In addition, confounding factors may not have been adequately controlled, as some potentially relevant confounders, such as socioeconomic status, were impossible to collect from children.

The present study demonstrated the negative effects of cSLE-related psychosocial variables on HRQoL, in that pain was shown to be associated with reduced HRQoL, and clinically significant pain (VAS >3) was a potential predictor of lower HRQoL scores, among patients with cSLE. Pain monitoring may provide valuable information for the identification of patients at high risk of reduced HRQoL, who may benefit from psychological therapies for effective pain control. Peer support and cognitive behavioural pain management have been recommended as strategies for effective relief of cSLE-associated pain symptoms.

In summary, pain due to systemic lupus erythematosus in the past week may significantly lower HRQoL in patients with cSLE. Further studies should be conducted to establish appropriate interventions to improve HRQoL, particularly in patients who are at higher risk, such as those experiencing cSLE-associated pain.

### Declaration of conflicting interests
The authors declare that there is no conflict of interest.

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| Characteristic | Health-related quality of life measure | PedsQL-GC Scale | PedsQL-RM scale |
|---------------|----------------------------------------|-----------------|-----------------|
|               | b | t | Statistical significance | b | t | Statistical significance |
| Age           | 1.03 | 1.01 | NS | 0.60 | 0.61 | NS |
| Sex           | ref. | ref. | | ref. | ref. | |
| Male          | | | | | |
| Female        | -16.15 | 2.26 | P = 0.029 | -10.78 | 1.56 | NS |
| Pain          | ref. | ref. | | ref. | ref. | |
| Yes           | -13.36 | 2.41 | P = 0.020 | -12.72 | 2.37 | P = 0.022 |
| BILAG score   | -0.72 | -0.72 | NS | 0.14 | 0.14 | NS |
| MD global     | 3.68 | 1.21 | NS | 0.31 | 0.11 | NS |

BILAG, British Isles Lupus Assessment Group disease activity index; MD global, physician global assessment of disease activity; PedsQL-GC, Pediatric Quality of Life Inventory Generic Core 4.0 scale; PedsQL-RM, Pediatric Quality of Life Inventory 3.0 Rheumatology Module.

**NS**, no statistically significant associations.
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