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Validation of the Cutaneous Lupus Erythematosus Disease Area and Severity Index and pSkindex27 for use in childhood-onset systemic lupus erythematosus

Ashwaq AlE'ed,[1] Pinar Ozge Avar Aydin,[2] Nora Al Mutairi,[3] Alhanouf AlSaleem,[3] Hafize Emine Sonmez,[4] Michael Henrickson,[2] Jennifer L Huggins,[2] Seza Ozen,[4] Sulaiman M Al-Mayouf,[3] Hermine I Brunner[2]

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AA'e and POAA contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Hermine I Brunner; hermine.brunner@cchmc.org

ABSTRACT

Objective To determine the measurement properties of the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the paediatric adaptation of the Skindex29 (pSkindex27) when used in childhood-onset SLE (cSLE).

Methods Patients with mucocutaneous involvement of cSLE were evaluated at the study entry and 6 months later. Besides the CLASI and pSkindex27, the Pediatric Quality of Life Inventory Generic Core scale (PedsQL-GC), its Rheumatology Module (PedsQL-RM), the SLE Disease Activity Index (SLEDAI) and the SLE Damage Index (SDI) were completed.

Results The CLASI and pSkindex27 had high internal consistency (both Cronbach $\alpha \geq 0.82$). Children were able to complete the pSkindex27, with self-report and caregiver proxy-reports showing excellent agreement (intraclass correlation coefficient=0.97). The CLASI Activity Score (CLASI-A) was strongly correlated with the mucocutaneous domain score of the SLEDAI as was the CLASI Damage Score (CLASI-D) with that of the SDI (both: Spearman correlation coefficients (r_s) >0.68). pSkindex27 summary scores were moderately correlated with those of the PedsQL-GC and PedsQL-RM (all: $r_s \geq |0.51|$), the CLASI-A and CLASI-D (both: $r_s \geq 0.64$), respectively. Patients who experienced a >50% improvement of the CLASI-A between study visits had significantly higher PedsQL-GC and pSkindex27 scores than those without improvement of mucocutaneous features.

Conclusion Both CLASI and pSkindex27 are useful assessment tools in cSLE, active and chronic mucocutaneous lesions and their changes over time can be measured using the CLASI and the pSkindex27 can capture the impact of mucocutaneous involvement on patient health-related quality of life.

INTRODUCTION

Mucocutaneous involvement is common with various forms of lupus.[1 2] The revised classification criteria of American College of Rheumatology (ACR) for SLE includes four mucocutaneous manifestations, namely malar rash, discoid rash, photosensitivity, and oral or nasopharyngeal ulcerations.[3] The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) has been developed to measure the degree of cutaneous manifestations of adults with isolated cutaneous lupus erythematosus (CLE) and SLE.[4–6] The CLASI features a skin activity summary score (CLASI-A) and damage summary score (CLASI-D). This index has a high inter-rater and intra-rater reliability and is responsive to change when used in adults with CLE and SLE.[5 7] The Skindex29 has been developed to capture the burden of skin pathology on health-related quality of life (HRQoL).[8–11] When used in adults with CLE and SLE, higher CLASI-A have been associated with lower HRQoL) as measured by the Skindex29.[11 12]

Skin lesions in childhood-onset SLE (cSLE) are frequent and similar in nature to those encountered by adults with SLE. In contrast to adults, isolated lupus-related skin lesions are rare in paediatric patients.[13–15] Further, previous research in cSLE supports that scarring alopecia and scarring rash are quite prevalent in cSLE and have been associated with markedly reduced HRQoL.[16] Despite the common occurrence of mucocutaneous involvement with cSLE, there are no validated indices to capture the degree of active inflammatory and chronic degenerative skin changes, nor are there specific scales to estimate the impact of skin involvement on HRQoL in children with cSLE. Before using scales in a given population, such as cSLE, it is necessary to establish their measurement properties. Especially for patient-completed questionnaires that have been developed for

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use in adults, paediatric adaptation may be required to account for developmental differences between adults and children. Hence, the objectives of this study in cSLE were to assess the feasibility, internal consistency, construct validity and responsiveness of the CLASI and the Skindex29, after potential adaption of the latter for use in children.

PATIENTS AND METHODS

Study design and participants

For this prospective longitudinal study, patients with cSLE were recruited from three paediatric rheumatology centres; Cincinnati Children's Hospital Medical Center (CCHMC), King Faisal Specialist Hospital and Research Center (KFSH-RC) and Hacettepe University Faculty of Medicine. The inclusion criteria were (1) a diagnosis of SLE as per the revised 1997 ACR classification criteria,[3] (2) a disease onset before the 18th birthday,[17] (3) signs of active and/or chronic mucocutaneous involvement due to cSLE as judged by the treating physician,[18] and (4) age ≤18 years at the time of study entry. Excluded were children with other connective tissue diseases besides cSLE.

Study procedures

There were two study visits approximately 6 months apart. Patient demographic information, current medications and results of routine laboratory testing (complete blood cell count with differential, blood chemistry, urinalysis, erythrocyte sedimentation rate, complement C3 and C4, anti–double-stranded DNA antibody levels) were extracted from the medical record at each study visit. Both patients with cSLE and one of their caregivers completed HRQoL scales. Physicians who were trained in the completion of the disease measures and examined the patients included in this study.

Cutaneous Lupus Erythematosus Activity and Severity Index

The CLASI measures both lupus-related mucocutaneous activity and damage.[4] Two summary scores can be calculated, the CLASI Activity Score (CLASI-A) and the CLASI Damage Score (CLASI-D). Besides mucocutaneous ulcerations and hair loss, active inflammatory skin pathology scored in the CLASI-A includes erythema and scale/hypertrophy in 13 distinct body areas (scalp, ears, nose and malar area, rest of face, V-area neck (frontal), post neck and shoulders, chest, abdomen, back and buttocks, arms, hands, legs, feet), mucous membrane lesions and alopecia due to active lupus. The CLASI-A (maximum score: 70; 0=no active mucocutaneous lesions) is the sum of the above item scores. Values between 1 and 9, 10 to 20, and ≥21 can be interpreted as mild, moderate and severe mucocutaneous inflammation, respectively. Further, a 20% decrease in the CLASI-A (CLASI-20%-responder) is considered a partial and a 50% reduction (CLASI-50%-responder) a major improvement of inflammatory skin lesions.[12] Based on the change of CLASI-A between visits, patients were categorised as CLASI-50%-responder, CLASI-20%-responder or CLASI non-responder, that is, if patients' CLASI-A improved by <20% between study visits or even worsened.

The CLASI-D (maximum score: 56; 0=no skin damage) considers dyspigmentation, skin scarring and/or panniculitis of the aforementioned 13 body areas. For the purpose of the analysis, we categorised skin damage to be absent (CLASI-D=0) or present (CLASI-D>0). Physicians completing the CLASI participated in at least one training session led by the developer the CLASI (V P Werth).

Skindex29 and its paediatric adaptation

The Skindex29 is a skin-specific HRQoL tool that has been validated for use in various cutaneous diseases, including CLE and SLE.[9] The questionnaire consists of 30 items grouped into three domains: emotions, symptoms and functioning. Each Skindex29 item is rated on a 5-point Likert scale (never, rarely, sometimes, often, all of the time). Item responses are transformed to range from 0 (no effect or never) to 100 (experienced all of the time). One Skindex item addresses side effects of treatment and is omitted from scoring. Three Skindex domain scores (emotions, symptoms, functioning) can be calculated from the unweighted mean of non-missing item scores. The Skindex29 summary score (Skindex29-total) reflects the unweighted average of three domain scores.[19 20] Like for the domain scores, higher Skindex summary score suggests more profound negative impact of skin disease on HRQoL. The Skindex29 has a high degree of internal consistency, test–retest reliability, and responsiveness to change in adults with SLE and CLE.[8 21 22]

Paediatric adaptation and translation of the instrument

There are two items in the functioning domain of the Skindex29 that the study investigators deemed age-inappropriate because these items were expected to create increased stress when answered by children and adolescents or when caregivers were asked to provide proxy-rating for their child with cSLE. One of these items pertained to sex life, and the other item questioned affection difficulty; both items were excluded from the paediatric adaptation of the Skindex (pSkindex27). Hence, the pSkindex27 consists of 28 items, one unscored item addressing adherence to treatment. The retained items were scored as in the Skindex29; pSkindex27 domain and overall summary scores (pSkindex27-total) were calculated in line with those of the Skindex29.

The principles of good practice for the translation and cross-cultural adaptation were applied to the translation process of the pSkindex27.[23] All participants completed the instrument in their native language (Arabic, English, Turkish).

Other measures completed by physicians

The SLE Disease Activity Index (version SLEDAI-2K; range 0–105; 0=inactive cSLE) was completed to measure global cSLE activity.[24 25] The SLEDAI includes the presence/absence of three items addressing active mucocutaneous involvement of cSLE, that is, rash, alopecia and mucosal

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ulcers. For this study, mucocutaneous (SLEDAI-MC; range 0–6) and extra-mucocutaneous domain scores (SLEDAI-extraMC; range 0–99) were calculated as well as the SLEDAI summary score (SLEDAI-total). The Systemic Lupus International Collaboration Clinics ACR Damage Index (SDI) was scored.[25 26] Besides the SDI summary score (SDI-total), we calculated the SDI skin domain score (SDI-MC; range: 0–3; 0=no skin-related damage), which encompasses the following items: scarring alopecia, extensive scarring or panniculum, and chronic skin ulceration.

Other measures completed by participants

The Pediatric Quality of Life Inventory (PedsQL) features child self-report and a parent proxy-report options. The Generic Core scale (PedsQL-GC) consists of 23 items comprising four health domains (physical, emotional, social and school functioning), and all items are scored on 5-point Likert scales from 0 (never) to 4 (almost always).[27] A *Physical Health Summary Score* (PhSS) can be calculated, which corresponds to the physical functioning domain score, and a *Psychosocial Health Summary Score* (PsSS) from the emotional, social and school functioning domain scores. Differences in the PedsQL-GC summary score (PedsQL-GC-total) exceeding 4.4 points are regarded clinically relevant.[4 27] The PedsQL Rheumatology Module (PedsQL-RM) captures the specific impact of rheumatic disease on HRQoL.[28] The PedsQL-RM includes 22 items grouped into five domains: pain and hurt, daily activities, treatment, worry and communication. Higher summary and domain scores (all, range 0–100) are reflective of better HRQoL. PedsQL-GC and the PedsQL-RM have construct validity and are responsive to change when used in cSLE.[29] Both patients and caretakers completed the PedsQL-GC questionnaire, but the PedsQL-RM was only completed by the patient with cSLE.

Statistical analysis

Validation strategies for the CLASI and pSkindex27 followed those previously suggested by the ACR.[30] The characteristics of the study cohort were summarised by descriptive statistics, continuous variables by mean±SD, and categorical variables by frequency (n) and percentage (%). Internal consistency of the CLASI and the pSkindex27 were estimated by Cronbach's alpha coefficient (α; range 0–1),[31] with α ≥0.70 considered as acceptable.[32] For construct validation, associations with traditional measures of cSLE (SLEDAI-extraMC, SLEDAI-MC, SDI-total, SDI-MC, PedsQL-GC, PedsQL-RM) were assessed using Spearman's correlation coefficients (r_s). The strength of the association was considered 'unrelated' for r_s values <0.2, 'weak' if between 0.20 and 0.40, 'moderate' between 0.40 and 0.60, or 'strong' if ≥0.60. We expected moderate to strong associations between the CLASI-A and the SLEDAI-MC and, respectively, the SDI-MC and the CLASI-D. We also anticipated that pSkindex27 scores were at least weakly correlated with those of the PedsQL scales. The strength of agreement between proxy-report given by a caregiver of a child with cSLE and patient self-report was measured via intraclass correlation coefficient (ICC) analysis, with ICC ≥0.90 considered as excellent agreement.[33] In support of the responsiveness of the CLASI, differences in the scores of traditional cSLE measures (SLEDAI-MC) and HRQoL scales (PedsQL-GC, PedsQL-RM) were tested for significant differences by response level (CLASI-50%-responder, CLASI-20%-responder, CLASI non-responder) using paired t-test. In support of the responsiveness of the pSkindex27, we investigated whether there were significant differences in pSkindex27 scores in CLASI responders. The statistical significance level was set at p value ≤0.05 (two-tailed). Statistical analyses were performed with IBM SPSS Statistics V.21.0 software for Windows (IBM).

RESULTS

Patient characteristics

A total of 48 patients (F:M=43:5) participated in the study. Their mean cSLE disease duration was 2.4 years (range 0–9.2); 47 of them completed two study visits separated by a mean of 6.5 months. Topical therapies for cSLE-associated skin lesions included corticosteroids and calcineurin inhibitors, and 67% of the patients (n=32) reported wearing sunblock regularly. Additional clinical details about the study cohort are provided in table 1. At baseline, 40 patients (83%=40/48) had mild (CLASI-A≤9), 5 (11%) had moderate (10<CLASI-A<20) and 3 (6%) had even severe mucocutaneous involvement (CLASI-A≥21). The most commonly present were inflammatory rash due to SLE (90%, n=43), malar rash (48%, n=23), discoid rash (40%, n=19), inflammatory alopecia (31%, n=15), photosensitivity (25%, n=12) and mucosal ulcers (15%, n=7).

Irreversible skin damage (CLASI-D>0) was observed in 40% of the patients (19/48) at baseline. All 19 patients with CLASI-D >0 had dyspigmentation; in seven children, there was also skin scarring which was combined with scarring alopecia in three of them; one patient had dyspigmentation and scarring alopecia but no skin scarring.

Patients treated at KFSH-RC were significantly younger (p=0.0001), had significantly higher CLASI-A (p=0.005), higher SLEDAI-MC (p=0.009), higher SLEDAI-total (p=0.037) and higher CLASI-D (p=0.001) as compared with patients recruited from the other two sites.

In table 2, HRQoL measurements at baseline are shown. Notably, pSkindex27 were numerically higher and PedsQL-GC scores (total and domain scores, PhSS, PsSS) were lower when using proxy-report as compared with self-report. Irrespective of the measure considered (pSkindex27, PedsQL-GC, PedsQL-RM), at baseline there were no significant differences in HRQoL of patients from different centres (p>0.05). There was a trend towards improvement (CLASI-A, SLEDAI-total) between the study visits (p>0.05) and only two patients (4%) experienced an increase of the CLASI-D between visits.

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Table 1 Demographics and disease features of the patients by site at visit 1*

Measure	All centres (N=48)	CCHMC (N=23)	HUMF (N=13)	KFSH-RC (N=12)
Women	43 (90%)	21 (91%)	12 (92%)	10 (83%)
Age, years	14. 6±3.6	16.3±1.4	15.4±3.0	10.4±3.9
Disease duration, years	2.4±2.3	2.1±2.0	2.4±2.8	3.1±2.4
Current medications				
Hydroxychloroquine	48 (100%)	23 (100%)	13 (100%)	12 (100%)
Prednisone	34 (71%)	14 (62%)	12 (92%)	8 (67%)
Dose (mg/day)	14.2±16.4	19.4±20.4	12.3±15.3	8.1±5.3
Pulse steroids	14 (29%)	2 (9%)	1 (8%)	11 (92%)
Immunosuppressants†	44 (92%)	21 (91%)	12 (92%)	11 (92%)
Disease activity				
SLEDAI-total	8.7±7.3	7.2±4.4	6.1±5.7	14.3±10.4
SLEDAI-MC	2.3±1.7	2.5±1.2	1.2±1.5	2.8±2.2
CLASI-A	5.7±7.1	3.1±2.7	4.5±4.7	11.8±11.0
Erythema	3.0±4.0	2.0±2.0	2.3±2.7	5.8±6.4
Scale/hypertrophy	1.2±2.3	0.2±0.7	1.1±1.3	3.4±3.6
Mucous membrane	0.2±0.4	0.1±0.3	0±0	0.4±0.5
Recent hair loss	0.3±0.5	0.2±0.4	0.3±0.5	0.5±0.5
Non-scarring alopecia	0.8±1.1	0.6±0.9	0.5±0.8	1.5±1.6
Disease damage				
SDI-total	0.7±1.1	0.4±0.6	0.6±1.2	1.3±1.4
SDI-MC	0.3±0.5	0.2±0.4	0.2±0.4	0.8±0.6
CLASI-D	3.0±5.8	0.6±1.7	1.7±2.0	8.9±9.0
Dyspigmentation‡	2.1±3.8	0.4±1.1	1.5±1.8	6.0±5.7
Scarring/atrophy/ panniculitis	0.5±1.1	0.1±0.2	0.3±0.8	1.4±1.9
Scarring alopecia	0.5±1.6	0.2±0.8	0±0	1.5±2.7

*Values are mean±SD or n (% of N).
†Immunosuppressants (number of patients treated with at least one immunosuppressant) were mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate, rituximab, leflunomide, belimumab and ciclosporin.
‡Dyspigmentation score is doubled if dyspigmentation usually remains visible for more than 12 months.
CCHMC, Cincinnati Children's Hospital Medical Center; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-AS, CLASI Activity Score; CLASI-DS, CLASI Damage Score; HUMF, Hacettepe University Faculty of Medicine; KFSH-RC, King Faisal Specialist Hospital and Research Center; SDI, Systemic Lupus International Collaboration Clinics American College of Rheumatology Damage Index; SDI-MC, SDI mucocutaneous domain; SLEDAI, SLE Disease Activity Index; SLEDAI-MC, SLEDAI mucocutaneous domain; cSLE, childhood-onset SLE.

Feasibility, internal consistency and quality of proxy-report

None of the patients or their caregivers had difficulties in completing the pSkindex27, and none refused to respond to any of the items. The average time needed to complete the pSkindex27 was 5 min.

There was acceptable internal consistency of the CLASI-A (α=0.84) and the CLASI-D (α=0.82). The same was true for the pSkindex27 across overall and within each domain (all: α>0.97). Proxy-reports of the pSkindex27-total showed excellent agreement with patient self-reports (ICC=0.97).

Construct validity

As summarised in table 3, the CLASI-A was strongly correlated with the SLEDAI-MC (r_s=0.68, p<0.01) and the CLASI-D with the SDI-MC (r_s=0.69, p<0.01), respectively. Conversely, neither the CLASI-A nor the CLASI-D were closely correlated with the SLEDAI-extraMC or the SDI-extraMC. The pSkindex27 domain and summary scores were at least weakly correlated with those of the PedsQL-GC and PedsQL-RM-total as well as their domain scores (all r_s≥|0.26|–|0.62|, p<0.01). An exception was the pain and hurt domain of the PedsQL-RM, which was unrelated to any of the pSkindex27 scores domain or overall summary scores (r_s<|0.17|; p>0.05).

There was significantly lower HRQOL (pSkindex27, PedsQL-RM, PedsQL-GC) with versus without skin damage (CLASI-D) (figure 1). Among patients with any

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Table 2 Health-related quality of life measures in the study cohort at visit 1*

Health-related quality of life measures	Patient self-report (N=43)	Caretaker proxy-report (N=45)	P values
pSkindex27 summary score	19.6±23.4 (0–84.3)	21.0±22.7 (0–72.2)	0.721
Emotions	22.0±26.7 (0–95.0)	22.7±24.8 (0–75.0)	0.851
Symptoms	21.3±21.8 (0–71.4)	21.7±20.1 (0–64.3)	0.919
Functioning	17.2±23.9 (0–90.0)	18.8±23.6 (0–75.0)	0.633
PedsQL-GC total score	71.0±18.6 (36.9–100)	67.5±20.3 (22.8–97.8)	0.074
PsSS	71.4±19.6 (33.3–100)	67.2±20.3 (23.3–100)	0.015
PhSS	70.9±22.8 (28.0–100)	68.7±24.6 (22.0–100)	0.538
PedsQL-RM total score	73.1±14.1 (45.5–100)		
Pain and hurt	75.9±27.2 (6.0–100)		
Daily activities	89.0±16.6 (45.0–100)		
Treatment	67.6±17.7 (32.0–100)		
Worry	60.7±25.8 (0–100)		
Communication	67.8±26.7 (8.0–100)		

*Values are mean±SDs (range).
PedsQL-GC, Pediatric Quality of Life Inventory Generic Core Module; PedsQL-RM, Pediatric Quality of Life Inventory Rheumatology Module; PhSS, Physical Health Summary Score; PsSS, Psychosocial Health Summary Score.

skin damage (CLASI-D>0), the PedsQL-GC-total was significantly lower among patients who had also scarring (skin and/or alopecia) as compared with those who only had skin dyspigmentation (mean±SE: 53.4±5.0 vs 74.2±5.5, p=0.022). Similar trends were observed for the PedsQL-RM-total and the pSkindex27-total (p>0.05).

Table 3 Relationship between the CLASI, pSkindex27 and other outcome measures at visit 1†

Summary and domain scores	CLASI		pSkindex27		
	CLASI-A	CLASI-D	Emotions	Symptoms	Functioning
SLEDAI-MC	0.68**	0.31*	0.50**	0.39**	0.50**
SLEDAI-extraMC	0.11	0.36*	0.06	0.04	0.12
SDI-MC	0.61**	0.69**	0.37*	0.44**	0.41**
SDI-extraMC	0.03	0.22	0.3	0.2	0.29
pSkindex27 summary score‡	0.64**	0.63**	0.96**	0.95**	0.92**
PedsQL-GC total‡	−0.35*	−0.39*	−0.62**	−0.51**	−0.60**
PsSS	−0.32*	−0.42**	−0.61**	−0.52**	−0.61**
PhSS	−0.18	−0.14	−0.35*	−0.27	−0.32*
PedsQL-RM total‡	−0.32*	−0.40**	−0.64**	−0.51**	−0.67**
Pain and hurt	−0.19	−0.09	−0.19	−0.17	−0.19
Daily activities	−0.18	−0.23	−0.53**	−0.50**	−0.49**
Treatment	−0.28	−0.45**	−0.51**	−0.47**	−0.61**
Worry	−0.36*	−0.43**	−0.54**	−0.43**	−0.59**
Communication	−0.22	−0.39*	−0.46**	−0.26	−0.42**

*p<0.05 level (2-tailed); **p<0.01 level (2-tailed).
†Values are Spearman's correlation coefficients.
‡Only patient self-reports are shown.
CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-A, CLASI Activity Score; CLASI-D, CLASI Damage Score; PedsQL-GC, Pediatric Quality of Life Inventory Generic Core Module; PedsQL-RM, Pediatric Quality of Life Inventory Rheumatology Module; PhSS, Physical health Summary Score; PsSS, Psychosocial health Summary Score; SDI-MC, SDI mucocutaneous domain; SDI-extraMC, Systemic Lupus International Collaboration Clinics American College of Rheumatology Damage Index extramucocutaneous domain score; SLEDAI-MC, SLEDAI mucocutaneous domain; SLEDAI-extraMC, Systemic Lupus Erythematosus Disease Activity Index extramucocutaneous domain.

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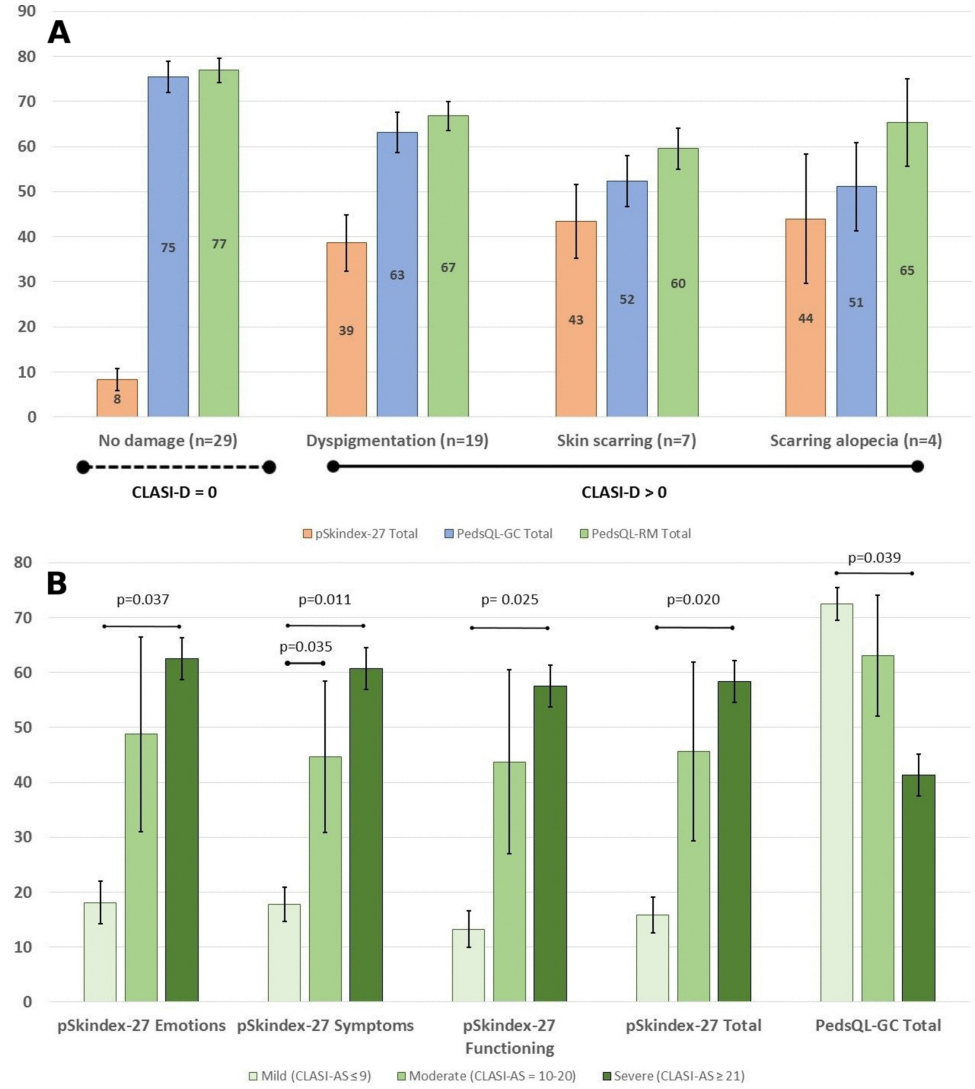


Figure 1 Impact of skin damage on health-related quality of life. Histograms represent means with SEs. (A) The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) damage summary scores (CLASI-D) of patients with absent or present damage have a significant negative impact on patient health-related quality of life as measured by the pSkindex27 and the Pediatric Quality of Life Inventory Generic Core scale (PedsQL-GC) (results from self-report are shown). (B) Different features of skin-related damage as measures by the CLASI are shown for their effects on health-related quality of life. The 29 patients without skin-related damage (CLASI-D=0) have higher health-related quality of life; skin scarring or scarring alopecia has a more profound negative effect on patients' health-related quality of life than dyspigmentation.

As depicted in figure 2, patients with mild mucocutaneous involvement (CLASI-A≤9) had significantly higher HRQoL as measured by the pSkindex27 or the PedsQL-GC-total (both: p<0.039) as compared with patients with severe mucocutaneous involvement (CLASI-A≥21) .

Responsiveness of the CLASI-A and pSkindex27

Absolute changes of the CLASI-A, CLASI-D and pSkindex27 by CLASI responder status between visits 1 and 2 are shown in table 4. Compared with CLASI non-responders (n=16), CLASI-20%-responders (n=31) and CLASI-50%-responders (n=17) had 7.1±3.7 (p<0.0001) and 7.5±4.0 (p<0.0001) higher CLASI-A scores, respectively. CLASI-20%-responders and CLASI-50%-responders had significantly higher PedsQL-GC-total than CLASI non-responders, with similar trends present for the PedsQL-RM (table 4). The pSkindex27-total was significantly lower among CLASI-50%-responders than CLASI non-responders. There was a trend towards lower pSkindex27-total among CLASI-20%-responders as compared with CLASI non-responders.

The mean pSkindex27-total among CLASI-50%-responders and CLASI-20%-responders were 20.5 points and 9.5 points lower than those of CLASI non-responders, respectively. Mean PedsQL-GC-total of CLASI-50%-responders and CLASI-20%-responders were >17 and >14 points higher compared with those of CLASI non-responders, respectively.

DISCUSSION

The results of this multicentre prospective longitudinal study support the reliability, construct validity

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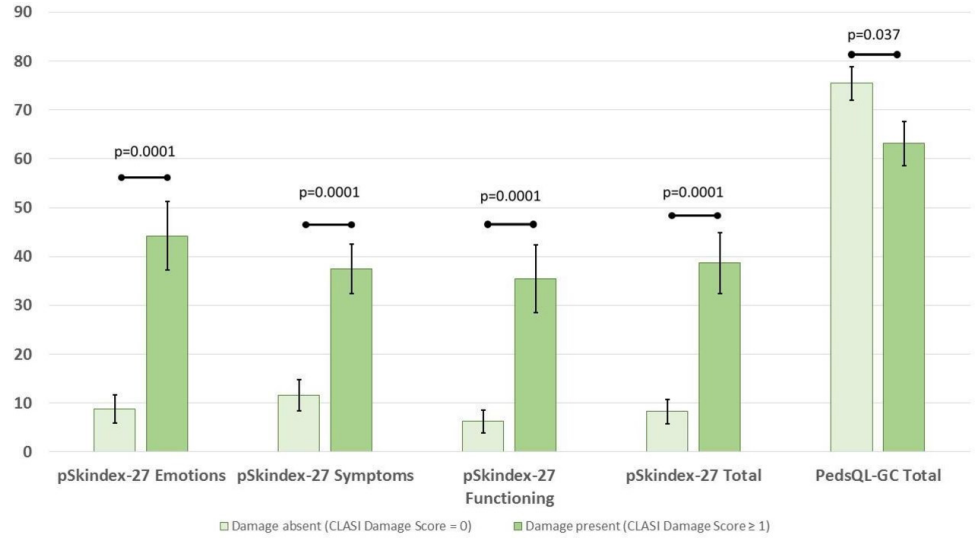


Figure 2 Impact of active mucocutaneous involvement on health-related quality of life with childhood-onset SLE. Histograms represent means with SEs. Patients are categorised as per the severity of their skin activity as measured by the CLASI-A. Lesser skin involvement is associated with higher health-related quality of life as measured by the pSkindex27 or the PedsQL-GC scale (results from self-report are shown). CLASI-A, Cutaneous Lupus Erythematosus Disease Areaand Severity Index Activity Score; CLASI-D, CLASI Damage Score; PedsQL-GC, PediatricQuality of Life Inventory Generic Core Module; PedsQL-RM, Pediatric Quality ofLife Inventory Rheumatology Module.

and responsiveness to change of the CLASI and the pSkindex27 when used in cSLE. Both tools were found to have a high internal consistency across a multiracial cSLE cohort with different degrees of skin involvement. Children and their caregivers had no difficulties in completing the pSkindex27, supporting its feasibility and ease of

Table 4 Responsiveness analysis of the CLASI and pSkindex27*

Mean±SD	–1 CLASI-50%-responders (n=17)	–2 CLASI-20%-responders (n=31)	–3 CLASI non-responders (n=16)	P values (1 vs 3)	P values (2 vs 3)
Visit 2					
CLASI-A	1.0±2.2	3.9±6.0	8.2±4.9	0.0001	0.001
CLASI-D	1.5±5.6	3.1±6.7	3.7±5.1	0.217	0.55
SLEDAI-MC	0.4±0.8	1.2±1.6	3.4±1.7	0.0001	0.0001
pSkindex27†	5.2±10.1	14.7±19.0	25.7±26.0	0.033	0.253
PedsQL-GC†	81.2±12.3	78.7±11.0	64.1±23.1	0.041	0.04
PhSS	81.3±15.1	80.0±15.6	63.8±28.0	0.064	0.073
PsSS	80.9±12.1	77.8±11.8	64.2±24.1	0.088	0.076
PedsQL-RM†	81.7±11.2	80.5±9.4	69.0±19.7	0.067	0.053
Change between visits					
CLASI-A	–3.2±4.0	–2.8±3.5	4.3±4.0	0.0001	0.0001
CLASI-D	–1.1±3.9	–0.2±3.2	1.1±2.4	0.245	0.523
SLEDAI-MC	–1.1±1.2	–0.8±1.4	0.6±1.6	0.006	0.005
pSkindex27†	–1.9±6.1	–2.8±11.8	1.4±14.1	0.377	0.281
PedsQL-GC†	3.9±16.1	4.5±15.1	–0.2±14.3	0.316	0.289
PedsQL-RM†	4.4±16.8	5.0±14.3	0.3± 11.0	0.567	0.424

*Mean±SD of summary scores are shown.
†Only patient self-reports are shown.
CLASI-A, Cutaneous Lupus Disease Area and Severity Index Activity Score; CLASI-D, CLASI Damage Score; PedsQL-GC, Pediatric Quality of Life Inventory Generic Core Module; PedsQL-RM, Pediatric Quality of Life Inventory Rheumatology Module, ; PhSS, Physical Health Summary Score; PsSS, Psychosocial Health Summary Score; SLEDAI-MC, SLE Disease Activity Index mucocutaneous domain.

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use. Evidenced also by the quality of proxy-report and the results of our validation analyses of the pSkindex27, the exclusion of two items of the adult Skindex seems not to have negatively influenced the excellent psychometric properties of the pSkindex27 when used in cSLE. Notably, we generated Arabic and Turkish translations for the pSkindex-27.

Our results support that the CLASI had both convergent and discriminant validity as its CLASI-A and CLASI-D were closely correlated with mucocutaneous manifestations of cSLE as measured by the SLEDAI and SDI, respectively, but not with others.

Different from the SLEDAI-MC, which only captures the presence versus absence of certain mucocutaneous lesions, the CLASI-A captures partial resolution and improvement of cSLE lesions, hence provides more detailed information regarding the course of cSLE-associated mucocutaneous involvement than what is captured by the SLEDAI.

Construct validity of the pSkindex27 is supported by its association with the scores of established HRQoL measures such as the PedsQL. Furthermore, pSkindex27 scores, which reflect the degree of negative impact of skin changes on HRQoL, were significantly higher in patients with moderate or severe as compared with those with only mild mucocutaneous manifestations. Notably, there was excellent agreement between patient self-report and parent proxy-report, suggesting that caregivers and patients are very similar in their interpretation of the impact of cSLE-associated skin disease on HRQoL.

Various approaches to assess the responsiveness of a scale have been reported in the medical literature.[34] To investigate the responsiveness of the CLASI to changes in active lesions, we used a method that compared differences in the mean scores of patients with various courses of their cSLE-associated skin disease. Children who experienced a reduction of the CLASI-A by at least 50% between study visits had significantly better HRQoL as measured by the PedsQL-GC and the pSkindex27. This supports that a 50% improvement of the CLASI-A is clinically relevant and our findings are also in line with a previous study in adults which defined a 50% reduction of the CLASI-A as representing a complete response to therapy.[35]

We would like to point out that even CLASI-20%-responders had over 10-point higher PedsQL-GC summary scores than CLASI non-responders, although differences in scores did not reach statistical significance. Given that absolute differences of PedsQL-GC-total summary scores exceeding 4.4 points are considered clinically relevant,[27] we suspect that even a 20% reduction of the CLASI-A has a markedly beneficial effect on patient HRQoL.

Both active and chronic mucocutaneous lesions as captured by the CLASI-A and CLASI-D, respectively, were found to have a profound negative impact on HRQoL with cSLE. This supports the results of an earlier study in cSLE[29] and stresses the importance of controlling mucocutaneous signs, even if they generally do not shorten the life span of a child with cSLE. While presence of skin damage negatively impacted HRQoL, previous investigations of adults with CLE failed to detect such a negative impact of skin damage (CLASI-D).[4 11] Additional research will be required to investigate this possibly differential effect of lupus-related skin damage on HRQoL in children as compared with adults.

Another difference between adults and children may be that mucocutaneous lupus features reduced only the functioning and emotional well-being as captured by the Skindex29 of adults with SLE.[12] While our results are in line with these observation from adults, HRQoL of children with cSLE was also negatively impacted by the symptoms of skin inflammation, namely burning, itching and irritation of the skin. Reasons for this difference are uncertain but might include developmental differences in coping with disease between children and adults as well as differences in the ethnic and racial make-up between cohorts.

While studies in population-based cSLE cohorts support that both disease activity and damage reduce the physical functioning aspects of HRQoL,[36] mucocutaneous involvement, as was present in all patients enrolled in this study, also had a negative impact on psychosocial aspects of patient HRQoL.

The CLASI has been used to measure the severity of mucocutaneous involvement and responsiveness to therapy in several adult studies mostly with CLE and a few studies included adults with SLE.[11 21 37] While isolated lupus skin without SLE[3] is common in adults, lupus-related skin lesions are usually associated with cSLE in children.[38–40] As multiorgan involvement is common with cSLE, children who participated in this study with high CLASI-A also often had extra-mucocutaneous disease activity.[41 42]

Strengths of this study include the intensive training of all participating physicians in the completion of the CLASI prior to study conduct, and the multiracial nature of our cohort. The latter supports that the CLASI and pSkindex27 can be used for patients with different cultural, racial and ethnic backgrounds.

Limitations of our study may be that only two patients experienced worsening of skin damage during the study. Thus, we were unable to evaluate the responsiveness of the CLASI-D or the pSkindex27 to increasing skin damage in cSLE. Additional research will be needed to address this scientific knowledge gap.

Further, we did not attempt to relate changes in medication use to change in CLASI scores, which could have added strength to this validation study. However, multiorgan involvement with cSLE is common and delineating medication use changes specifically limited to mucocutaneous manifestations would have limited the interpretation of changes in medication use over time.

Our study design could have been strengthened by also including other paediatric indices of skin-specific HRQoL, such as the Dermatology Life Quality Index[43] and by performing more extensive studies in the validation

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of the translations of the pSkinDex27 developed for this study. Nonetheless, investigators have vast experience in cross-validation of questionnaires and proven methods were used.[44–46] Further, compared with previous studies of population-based cSLE cohorts, the patients enrolled in this study had lower HRQoL as measured by the PedsQL.[28 29] We do not think that this influenced the results of our validation studies. Rather, we believe that differences in HRQoL between the study cohort and population-based cohorts are due to this study's eligibility criteria and reflect the profound burden of mucocutaneous involvement in cSLE.

To the best of our knowledge, this is the first study assessing the usefulness of the CLASI and pSkindex27 in cSLE. Our findings suggest that both scales have superior measurement properties that may allow the use of the CLASI and pSkindex27 in future epidemiological and treatment studies of children with cSLE. However, additional validation will be necessary to fully delineate the measurement properties of both the CLASI and the pSkindex27.

Author affiliations
[1]Department of Pediatrics, College of Medicine, Qassim University, Buraidah, Saudi Arabia
[2]Department of Pediatrics, University of Cincinnati College of Medicine, Division of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[3]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[4]Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Contributors AAE: study design, data collection, manuscript preparation, final approval of manuscript. POAA: data collection, statistical analysis, manuscript preparation, final approval of manuscript. NAM: data collection, manuscript preparation, final approval of manuscript. AAS: data collection, manuscript preparation, final approval of manuscript. HES: data collection, manuscript preparation, final approval of manuscript. MH: data collection, manuscript preparation, final approval of manuscript. JLH: data collection, manuscript preparation, final approval of manuscript. SO: data collection, manuscript preparation, final approval of manuscript. SMA-M: data collection, manuscript preparation, final approval of manuscript. HIB: study design, data collection, statistical analysis, manuscript preparation, final approval of manuscript.

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