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# Usefulness of the lupus low disease activity state as a treatment target in childhood-onset SLE

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## ABSTRACT

**Objective** Treat-to-target (T2T) strategies are advocated to improve prognosis in childhood-onset SLE (cSLE). Proposed T2T states include SLEDAI score of ≤4 (SLEDAI-LD), limited corticosteroid use (low-CS), and lupus low disease activity state (LLDAS). We sought to compare T2T states for their association with cSLE prognosis under consideration of relevant disease characteristics such as pre-existing damage, race and lupus nephritis (LN).

**Methods** Longitudinal data from 165 patients enrolled in the Cincinnati Lupus Registry were included. LN presence was based on renal biopsy, and patients were followed up until 18 years of age.

**Results** The 165 patients (LN: 45, white: 95) entered the registry within a median of 0 (IQR: 0–1) year post diagnosis and were followed up for a median of 4 (IQR: 2–5) years during which 80%, 92% and 94% achieved LLDAS, low-CS and SLEDAI-LD. Patients with LN were significantly less likely to achieve any T2T state (all p≤0.03) and required a significantly longer time to reach them (all p<0.0001). Over the study period, patients maintained low-CS, SLEDAI-LD or LLDAS for a median of 76% (IQR: 48%–100%), 86% (IQR: 55%–100%) or 39% (IQR: 13%–64%) of their follow-up. Significant predictors of failure to maintain LLDAS included LN (p≤0.0062), pre-existing damage (p≤0.0271) and non-white race (p≤0.0013). There were 22%, 20% and 13% of patients who reached SLEDAI-LD, CS-low and LLDAS and nonetheless acquired new damage. Patients with LN had a higher risk of new damage than patients without LN even if achieving low-CS (p=0.009) or LLDAS (p=0.04).

**Conclusions** Patients with LN and pre-existing damage are at higher risk of increased future damage acquisition, even if achieving a T2T state such as LLDAS. Among proposed common T2T states, the LLDAS is the hardest to achieve and maintain. The LLDAS may be considered the preferred T2T measure as it conveys the highest protection from acquiring additional disease damage.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lupus low disease activity state (LLDAS) is achievable in the paediatric population and is associated with reduced risk of flare and accumulation of damage.
⇒ LLDAS is harder to achieve in adults with lupus nephritis.
⇒ LLDAS is a useful long-term disease state measure when used in clinical trials of adults with SLE.

### WHAT THIS STUDY ADDS

⇒ Patients with childhood-onset SLE (cSLE) who achieve LLDAS are at a lower risk of acquiring new damage compared with those who only reach other treat-to-target (T2T) states.
⇒ Even if LLDAS is achieved, patients with cSLE with kidney involvement versus those without are at higher risk of damage accumulation.
⇒ In cSLE, pre-existing damage is a risk factor for further damage accumulation even if LLDAS is achieved.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ LLDAS is achievable and should be the preferred T2T strategy in patients with cSLE.
⇒ Patients with pre-existing damage and lupus nephritis likely need further disease-modifying strategies due to their increased risk of damage.
⇒ LLDAS may be considered the preferred T2T goal, given that reaching and maintaining LLDAS minimise the risk of damage accumulation during the course of cSLE.

## INTRODUCTION

SLE is a chronic multisystem inflammatory disease that continues to result in considerable morbidity and mortality.[1] Systemic corticosteroids are commonly used to control major organ involvement with SLE. Patients with childhood-onset SLE (cSLE)[2] have been found to have more multiorgan involvement, including lupus nephritis (LN), and persistently active disease when compared with adult-onset SLE. Presence of kidney involvement (or LN) is a known risk factor for poor prognosis and more common in paediatric than adult SLE cohorts.[3 4]

In recent years, treat-to-target (T2T) strategies for managing SLE and cSLE have been formulated to improve disease outcomes.[5–7]

Proposed T2T goals in cSLE have traditionally been low disease activity and limited use of corticosteroid (CS).[3 6–8] In an effort to minimise damage acquisition associated with chronic exposure to CS,[9–11] clinicians treating cSLE attempt to minimise CS exposure while maintaining low disease activity states.[9 12] In this context, the use of hydroxychloroquine and immunosuppressants other than CS is considered protective against disease damage and higher cumulative CS exposure.[9 13]

To operationalise the aforementioned concept, the lupus low disease activity state (LLDAS) was developed and proposed as a T2T goal of adults with SLE.[14] LLDAS requires patients to tolerate immunosuppressive medication and require no more than low-dose CS to maintain a low level of SLE activity. Indeed, achievement and maintenance of LLDAS in adults are associated with reduced damage acquisition and improved survival.[15 16]

LLDAS is more difficult to achieve in adults with LN.[17 18] Nonetheless, despite more frequent kidney involvement, there is initial evidence that LLDAS can be achieved in cSLE and is associated with better cSLE prognoses.[19 20]

We aimed to further evaluate LLDAS as a T2T measure in cSLE that limits damage acquisition and to compare the LLDAS to more traditional T2T measures, such as low disease activity and limited use of CS, with specific consideration of the impact of kidney involvement.

## METHODS

### Patients

Patients enrolled in the Cincinnati Children's Lupus Registry between January 2008 and May 2021 (IRB 2008–0635) were included in this study,[21 22] after recruitment in the rheumatology clinics. Patients fulfilled either the 1997 American College of Rheumatology (ACR) criteria[23] or the 2019 European League Against Rheumatism/ACR classification criteria of SLE[24 25] and were evaluated in the rheumatology clinic at least twice for cSLE. Given our focus on damage development in the paediatric age range, we included only patients with cSLE with disease onset prior to 16 years of age and censored follow-up data once patients reached the age of 18 years.

Data extracted comprised age at diagnosis, age at visit, weight, sex, self-reported race and ethnicity, disease activity as measured by the SLE Disease Activity Index V.2K (SLEDAI-2K),[26] disease activity in new organ system since last visit (yes/no), the summary score but not the item scores of disease damage as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI),[9 27] physician global assessment of cSLE activity measured on a 21-circle visual analogue scale (range: 0–10, 0=inactive), treatment information such as daily prednisone equivalent dose, and use and tolerance of immunosuppressive medications (yes/no). The latter was based on surveillance laboratory testing and physician documentation. Patients were identified as having LN based on International Classification of Diseases (ICD), 9th Revision, or ICD, 10th Revision, diagnosis codes,[28] with confirmation based on kidney biopsy. All patients who had or newly developed LN during the study follow-up were categorised as having LN. Data were recorded and managed using Research Electronic Data Capture (Vanderbilt University, Nashville, Tennessee, USA),[29] a secure, web-based application designed to support data capture for research.

### Outcome measures considered in this study

#### T2T states

We evaluated three T2T states for their relationship to disease damage, which we considered the longer-term prognostic outcome in this study. T2T states were (1) controlled cSLE activity, defined as a SLEDAI score of ≤4 (SLEDAI-LD);[6 7 30] (2) limited corticosteroid use (low-CS), defined as daily prednisone equivalent doses of 0.15 mg/kg body weight, up to a maximum of 7.5 mg/day, whichever was less;[6 7 30] and (3) LLDAS, defined as the presence of all of the following: SLEDAI-2K score of <4 without activity in major organ systems, without haemolytic anaemia or gastrointestinal activity, no new features of disease activity compared with previous assessment, Physician Global Assessment (PGA) score of <1 (scale 0–3), daily prednisone equivalent dose of <7.5 mg and well-tolerated standard maintenance doses of immunosuppressives.[14]

#### Disease damage

Disease damage, defined as 'non-reversible change, not related to inflammation, occurring since the diagnosis of SLE', was ascertained by medical record review.[27] The SDI enumerates the accumulation of damage that has occurred since the diagnosis of SLE in 12 organ systems.[31] The maximum SDI score is 49, and a score of 0 represents absence of disease damage (damage-free). Originally developed for adults with SLE, the SDI has been validated for use in cSLE.[9] Further, it has been shown that pre-existing damage is a risk factor for further damage acquisisiton in cSLE and SLE.[32 33]

### Statistical analysis

The baseline distributions of patient demographic and disease characteristics were described by reporting frequencies for categorical data, means and SD or SEs for interval scaled or medians, and first quartile (Q1) and third quartile (Q3) for ordinal scaled data, respectively, based on distribution of values, and grouped by kidney involvement (LN group vs no-LN group). $\chi^2$ was used for categorical variables, and Wilcoxon rank-sum test was used for ordinal or interval scaled variables to compare the baseline characteristics between the patients with LN and patients without LN. We used linear transformation to scale visual analog scale (VAS) values of PGA (range: 0–10)[34 35] in our registry to a scale to fit the traditional PGA measure used in the LLDAS (range: 0–3).[14 31] The first achievement of each and any T2T state (SLEDAI-LD, low-CS and LLDAS) was identified for each patient from

**Table 1** Baseline characteristics of 165 patients with childhood-onset SLE*

| Variables | Total cohort (N=165) | LN group (N=45) | No-LN group (N=120) | P value LN group versus no-LN group† |
|---|---|---|---|---|
| Demographics | | | | |
| Female gender | 137 (83) | 37 (82) | 100 (83%) | 0.87 |
| White race | 95 (58) | 18 (40) | 77 (64) | 0.03 |
| Hispanic ethnicity | 5 (3.0) | 1 (2.2) | 4 (3.3) | 0.77 |
| Age at diagnosis (years) | 13 (12, 15) | 13 (12, 14) | 14 (12, 15) | 0.39 |
| Disease duration at baseline (years) | 0 (0, 1) | 0 (0, 2) | 0 (0, 1) | 0.06 |
| Follow-up duration (years) | 4 (2, 5) | 4 (3, 6) | 3 (2, 5) | 0.03 |
| Weight (kg) | 56.5 (46.8, 63.6) | 58.65 (50, 63.7) | 56 (45.5, 63.6) | 0.35 |
| Medication use | | | | |
| Hydroxychloroquine | 132 (80) | 36 (80) | 96 (80) | 1.00 |
| Minimal oral prednisone use | 105 (64) | 20 (44) | 85 (71) | 0.0017 |
| Intravenous methylprednisolone use | 11 (6.7) | 3 (6.7) | 8 (6.7) | 1.00 |
| Oral prednisone dose (mg/day) | 0 (0, 15) | 10 (0, 30) | 0 (0, 10) | 0.0021 |
| Oral weight-adjusted prednisone dose (mg/kg/day) | 0 (0, 0.32) | 0.24 (0, 0.79) | 0 (0, 0.16) | 0.0014 |
| Immunosuppressants† | 45 (27) | 14 (31) | 31 (26) | 0.50 |
| Disease activity/damage | | | | |
| SLEDAI-2K score* | 4 (1, 8) | 9 (4, 18) | 2 (0, 4.5) | <0.0001 |
| SDI score* | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.096 |
| SDI score=0 (%) | 141 (86) | 35 (78) | 106 (88) | 0.087 |
| T2T state | | | | |
| Presence of SLEDAI-LD | 105 (64) | 15 (33) | 90 (75) | <0.0001 |
| Use of low-CS | 103 (62) | 20 (44) | 83 (69) | 0.0035 |
| Presence of LLDAS | 48 (29) | 7 (16) | 41 (34) | 0.0191 |
| Any of the T2T states | 131 (79) | 27 (60) | 104 (87) | 0.0002 |

*Values are n (%) or median (25th, 75th percentile) unless stated otherwise; Wilcoxon two-sample test was used for continuous variables, and $\chi^2$ test was used for categorical variables.
†Immunosuppressants were cyclophosphamide; mycophenolate mofetil; methotrexate, azathioprine, cyclosporine and leflunomide; rituximab, tocilizumab, abatacept and belimumab.
CS, corticosteroid; LLDAS, lupus low disease activity state; LN, lupus nephritis; low-CS, limited corticosteroid use; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, SLE Disease Activity Index V.2K; SLEDAI-LD, SLEDAI score of ≤4; T2T, treat-to-target.

the time of registry entry. Kaplan-Meier curves were used to assess the time to onset of low-CS, SLEDAI-LD, LLDAS or any of the T2T states, stratified by (1) presence of LN and (2) pre-existing damage (SDI score >0) at the time of registry entry. Log-rank test was used to evaluate the bivariate relationship between the baseline demographic and disease characteristics to the time of reaching a given T2T state. Further, we summarised the maintenance of T2T states during the follow-up by calculating frequency of patient encounters in which they remained in the T2T state, after achieving the T2T state initially. The relationship of T2T states with baseline covariates was compared using Wilcoxon rank-sum test for categorical variables and the Spearman's correlation for continuous variables. Finally, we investigated the time from baseline to T2T-state achievement and to acquisition of additional damage. Candidate predictors considered were LN yes/no, age, weight, gender, race (white/non-white), SDI=0 at baseline, and duration of cSLE since diagnosis at baseline. Stepwise multivariable Cox proportional hazard regression with entry p value of 0.3 and stay p value of 0.1 was used to identify risk factors to each of the responses. All statistics were performed using SAS V.9.4, and two-sided p values of <0.05 were considered statistically significant.

## RESULTS

### Patients

A total of 165 patients were included in the analysis, 45 patients with kidney involvement (LN group) and 120 without kidney involvement (no-LN group). Of the 165 patients, 100 patients (LN group: 23) entered the registry

**Table 2** Frequency and time in years to reaching a T2T state during the follow-up period

| | Total cohort (N=165) | | LN group (N=45) | | No-LN group (N=120) | | P value LN group versus no-LN group* | |
|---|---|---|---|---|---|---|---|---|
| | n (% of N) | Median (25th, 75th percentiles) time to event | n (% of N) | Median (25th, 75th percentiles) time to event | n (% of N) | Median (25th, 75th percentiles) time to event | Frequency of event | Median time to event |
| Presence of SLEDAI-LD | 159 (94) | 0 (0, 0.24) | 40 (89) | 0.23 (0, 0.61) | 119 (99) | 0 (0, 0) | 0.002 | <0.0001 |
| Low-CS | 151 (92) | 0 (0, 0.67) | 37 (82) | 0.28 (0, 1.65) | 114 (95) | 0 (0, 0.41) | 0.009 | <0.0001 |
| Presence of LLDAS | 132 (80) | 0.53 (0, 1.61) | 30 (67) | 1.11 (0.49, NE) | 102 (85) | 0.27 (0, 1.00) | 0.009 | <0.0001 |
| Presence of any T2T state | 161 (98) | 0 (0, 0) | 42 (93) | 0 (0, 0.48) | 119 (99) | 0 (0, 0) | 0.03 | <0.0001 |

*P values are from $\chi^2$ test or Fisher's exact test as appropriate, or −2 log-rank test.
CS, corticosteroid; LLDAS, lupus low disease activity state; LN, lupus nephritis; low-CS, limited corticosteroid use; NE, not estimable; SLEDAI-LD, SLEDAI score of ≤4; T2T, treat-to-target.

at the time of diagnosis with cSLE. LN developed after a mean±SD of 2.38 (2.32) years since the diagnosis of cSLE. Table 1 compares the baseline demographics of these two groups. Groups significantly differed in disease activity, race (white/non-white) and the presence of T2T states at baseline. There were no differences in hydroxychloroquine use between groups, but the LN group was treated with higher absolute and weight-adjusted daily doses of prednisone. There were only few patients with Asian racial background. At baseline, there were 141 patients who were damage-free (SDI score=0), including 35 patients (35/45=78%) in the LN group.

Follow-up data were 2166 patient visits, representing a total of 536 patient-years (PY; LN group: 154 PY, no-LN group: 382 PY). Notably, the follow-up period of the LN group was significantly longer than that of the no-LN group (LN group vs no-LN group: 4 (IQR: 3–6) vs 3 (IQR: 2–5); p=0.03). During the follow-up, the median numbers of visits were 12 (IQR: 8–19) in the LN group and 11 (IQR: 7–6) in the no-LN group, resulting in a comparable median number of visits per year of follow-up of 4.6 (IQR: 3.2–5.8) and 3.9 (IQR: 3.1–5.3), respectively. Additional details about the cohort are provided in online supplemental table S1.

## Frequency and time to achievement of T2T status

During the study follow-up, almost all patients (161/165, 98%) achieved at least one of the T2T states mostly during the initial year of follow-up (table 2). Of the 165 patients, 6 patients (3.6%) failed to achieve SLEDAI-LD; 14 patients (8.5%) failed to achieve low-CS; and 33 patients (20%) did not reach LLDAS during the follow-up. The most common reason for a patient in SLEDAI-LD to not also achieve LLDAS was new disease activity (data not shown). As shown in table 2, compared with the no-LN group, the LN group was significantly less likely to achieve any of the

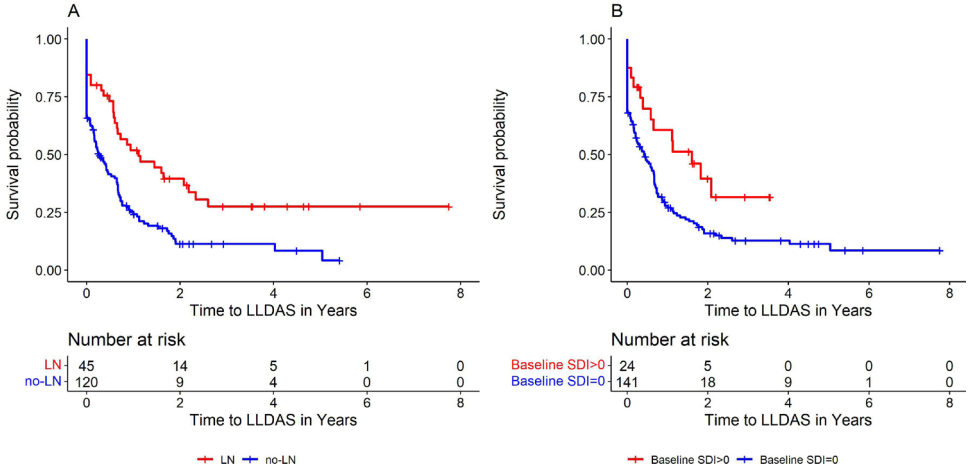


**Figure 1** (A) Comparison of the time trajectories for achieving LLDAS for patients with cSLE with kidney involvement (denoted as LN) compared with those without kidney involvement (denoted as no-LN). Patients with cSLE and kidney involvement required a significantly longer time after registry entry to achieve LLDAS (p<0.0001). (B) Comparison of the time trajectory to reaching LLDAS in those patients with early disease damage as indicated by a baseline SDI score of more than 0 at registry entry compared with patients with cSLE who were damage-free (baseline SDI=0). cSLE, childhood-onset SLE; LLDAS, lupus low disease activity state; LN, lupus nephritis; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

**Table 3** Statistically significant predictors of achieving T2T states in univariate analysis

| Response variables | Effect | HR estimate (95% CI) | P value |
|---|---|---|---|
| Presence of SLEDAI-LD | LN group versus no-LN group | 0.503 (0.345 to 0.735) | 0.0004 |
| Low-CS | LN group versus no-LN group | 0.600 (0.405 to 0.888) | 0.01 |
| | Non-white versus white | 0.631 (0.446 to 0.892) | 0.009 |
| Presence of LLDAS | LN group versus no-LN group | 0.547 (0.360 to 0.833) | 0.005 |
| | Non-white versus white | 0.710 (0.495 to 1.019) | 0.06 |
| Presence of any T2T states | LN group versus no-LN group | 0.647 (0.445 to 0.940) | 0.02 |

CS, corticosteroid; LLDAS, lupus low disease activity state; LN, lupus nephritis; low-CS, limited corticosteroid use; SLEDAI-LD, SLEDAI score of ≤4; T2T, treat-to-target.

T2T states (all p≤0.03) and required a significantly longer time to achieve them (all p<0.0001).

Figure 1A compares the time trajectories to achieving LLDAS for the LN group to the no-LN group. The 24 patients who had SDI scores of >0 at baseline were less likely (p=0.046) than those without damage at baseline (n=141) to achieve LLDAS; patients with SDI scores of >0 at baseline also required a significantly longer time to achieve low-CS (p<0.0001), SLEDAI-LD (p=0.0026) and LLDAS (p=0.0056, figure 1B), respectively.

### Predictors of achieving T2T states

In the univariate analysis, renal involvement, presence of baseline damage and non-white race were all statistically significant predictors of achievement of low-CS (p values all <0.03), whereas neither sex, age at diagnosis (or at study baseline) nor patient weight predicted achievement of low-CS during the study follow-up. The same predictors were identified for achievement of LLDAS (table 3). Multivariable analyses confirmed the relevance of LN and non-white race as important predictors of low-CS and LLDAS, respectively. In the univariate and multivariable analyses, only the presence of LN during the follow-up period (p<0.001) was identified as a significant predictor of SLEDAI-LD.

### Factors affecting maintenance of T2T state

Analysis of the maintenance of T2T states during the study follow-up was restricted to the 144 patients with a follow-up of >1 year. These 144 patients with cSLE spent a median proportion of the study period of 0.76 (IQR: 0.48–1.0), 0.86 (IQR: 0.55–1.0) and 0.39 (IQR: 0.13–0.64) in low-CS, SLEDAI-LD and LLDAS, respectively. Table 4 summarises the relevance of certain baseline factors for the maintenance of each T2T state in the univariate analysis and applied Wilcoxon rank-sum test, which evaluated statistically significant differences between groups (table 4). Compared with the no-LN group, the LN group was significantly less likely to achieve any T2T state (all p≤0.0062). A diagnosis of LN during the follow-up period, presence of baseline damage and non-white race all made a patient less likely to maintain T2T states during the study (all p<0.05). Entering the registry at the time of diagnosis as opposed to later did not influence maintenance of LLDAS or SLEDAI-LD during the study.

### Damage acquisition under consideration of kidney involvement during the follow-up

Of the 141 (85%) patients who were without damage (SDI=0) at baseline, 112 patients (79%) remained damage-free at the end of the follow-up period. As depicted in figure 2, damage trajectories differed significantly with LN status (log-rank p=0.0004). The risk of acquiring damage by the end of 1 year of follow-up was 37% in the LN and 21% in the no-LN group (Kaplan-Meier estimate±SE): 0.37±0.07 vs 0.21±0.04, p=0.0012). Based on stepwise selection in multivariable Cox proportional hazard modelling, having LN was the only significant risk factor of damage acquisition (HR=2.29, p=0.001). There was a trend towards non-white race to be a risk factor for new damage at 1 year of study follow-up (HR=1.67, p=0.08). Irrespective of whether the patient entered the study at the time of diagnosis or not, the LN group acquired more damage more rapidly compared with the no-LN group (online supplemental figure S1).

### Damage acquisition after achievement of T2T states

Additional damage (ie, increase in SDI score) during the follow-up occurred in 22% (35/158) of patients who achieved SLEDAI-LD and in 20% (30/150) of patients who achieved low-CS. For patients achieving LLDAS, the risk of acquiring additional damage was 13% (17/131). There was no significant difference in the risk of acquiring additional damage by LN status after achieving SLEDAI-LD (LN vs no-LN: 13/40 vs 22/118, p=0.10; figure 3A). Patients with LN had a significantly higher risk of acquiring damage after achieving low-CS (LN vs no-LN group: 13/37 vs 17/113, p=0.009; figure 3B) or LLDAS (LN vs no-LN: 7/30 vs 10/101, p=0.04; figure 3C). Besides presence of damage at baseline (HR=4.67, p=0.03), stepwise multivariable Cox proportional hazard model among those patients who achieved LLDAS identified the presence of LN (HR=3.4, p=0.02) as the strongest predictors of subsequent damage acquisition during the study follow-up. Conversely, presence of LLDAS at baseline was a significant protective factor for the acquisition of additional damage (HR=0.312, p=0.02).

## DISCUSSION

With this study, we add to the growing literature of the importance of achieving T2T states as a strategy to optimise cSLE care that yields better cSLE prognosis. Among the T2T goals evaluated, achievement and maintenance of LLDAS was associated with the lowest risk of subsequent acquisition of disease damage. Further, we identify

**Table 4** Baseline predictors of maintaining the T2T states during the study in patients with at least 1 year of follow-up*

| | | Low-CS | | SLEDAI-LD | | LLDAS | | Any T2T | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Median (IQR) proportion of follow-up in state† | P value | Median (IQR) proportion of follow-up in state) | P Value | Median (IQR) proportion of follow-up in state | P value | Median (IQR) proportion of follow-up in state | P value |
| Renal involvement | | | | | | | | | |
| No | 103 | 0.86 (0.57–1.0) | | 0.93 (0.73–1.0) | | 0.41 (0.22–0.67) | | 1.00 (0.88–1.0) | |
| Yes | 41 | 0.50 (0.18–0.91) | | 0.55 (0.29–0.83) | | 0.17 (0–0.5) | | 0.80 (0.47–1.0) | |
| Race | | | | | | | | | |
| Non-white | 63 | 0.60 (0.25–0.88) | <0.0001 | 0.71 (0.33–1.0) | 0.0026 | 0.27 (0.04–0.5) | 0.0013 | 0.9 (0.54–1.0) | 0.0007 |
| White | 81 | 0.94 (0.63–1.0) | | 0.88 (0.76–1.0) | | 0.43 (0.25–0.71) | | 1.00 (0.9–1.0) | |
| Registry entry at the time of diagnosis | | | | | | | | | |
| No | 54 | 0.77 (0.36–1.0) | 0.7926 | 0.78 (0.5–1.0) | 0.1027 | 0.38 (0.09–0.73) | 0.9357 | 1.00 (0.68–1.0) | 0.2542 |
| Yes | 90 | 0.75 (0.5–1.0) | | 0.88 (0.62–1.0) | | 0.4 (0.15–0.62) | | 1.00 (0.85–1.0) | |
| SDI score of 0 at baseline | | | | | | | | | |
| No | 21 | 0.57 (0.11–0.73) | 0.0033 | 0.63 (0.27–0.87) | 0.0175 | 0.26 (0–0.4) | 0.0271 | 0.83 (0.5–1.0) | 0.0033 |
| Yes | 123 | 0.82 (0.52–1.0) | | 0.87 (0.62–1.0) | | 0.40 (0.15–0.67) | | 1.00 (0.84–1.0) | |
| In low-CS at baseline | | | | | | | | | |
| No | 54 | 0.46 (0.1–0.67) | <0.0001 | 0.67 (0.3–0.93) | <0.0001 | 0.22 (0–0.4) | <0.0001 | 0.79 (0.5–0.97) | <0.0001 |
| Yes | 90 | 1.00 (0.73–1.0) | | 0.91 (0.75–1.0) | | 0.50 (0.26–0.71) | | 1.00 (0.96–1.0) | |
| In SLEDAI-LD at baseline | | | | | | | | | |
| No | 53 | 0.59 (0.19–0.91) | <0.0001 | 0.55 (0.29–0.8) | <0.0001 | 0.17 (0–0.4) | <0.0001 | 0.78 (0.5–0.96) | <0.0001 |
| Yes | 91 | 0.90 (0.6–1.0) | | 1.00 (0.83–1.0) | | 0.47 (0.27–0.71) | | 1.00 (0.97–1.0) | |
| In LLDAS at baseline | | | | | | | | | |
| No | 103 | 0.68 (0.35–0.93) | <0.0001 | 0.80 (0.46–0.93) | <0.0001 | 0.27 (0.05–0.44) | <0.0001 | 0.92 (0.68–1.0) | <0.0001 |
| Yes | 41 | 1.00 (0.88–1.0) | | 1.00 (0.86–1.0) | | 0.71 (0.48–.85) | | 1.00 (1.0–1.0) | |
| In any of the T2T states at baseline | | | | | | | | | |
| No | 29 | 0.30 (0.08–0.63) | <0.0001 | 0.40 (0.25–0.67) | <0.0001 | 0.10 (0–0.25) | <0.0001 | 0.59 (0.4–0.78) | <0.0001 |
| Yes | 115 | 0.92 (0.59–1.0) | | 0.92 (0.75–1.0) | | 0.43 (0.26–.69) | | 1.00 (0.92–1.0) | |

*P values from univariate analysis and applied Wilcoxon rank-sum test to evaluate statistically significant differences between groups.
†1.0 reflects 100% median of 100% of follow-up time of 1 or more years.
CS, corticosteroid; LLDAS, lupus low disease activity state; low-CS, limited corticosteroid use; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-LD, SLEDAI score of ≤4; T2T, treat-to-target.

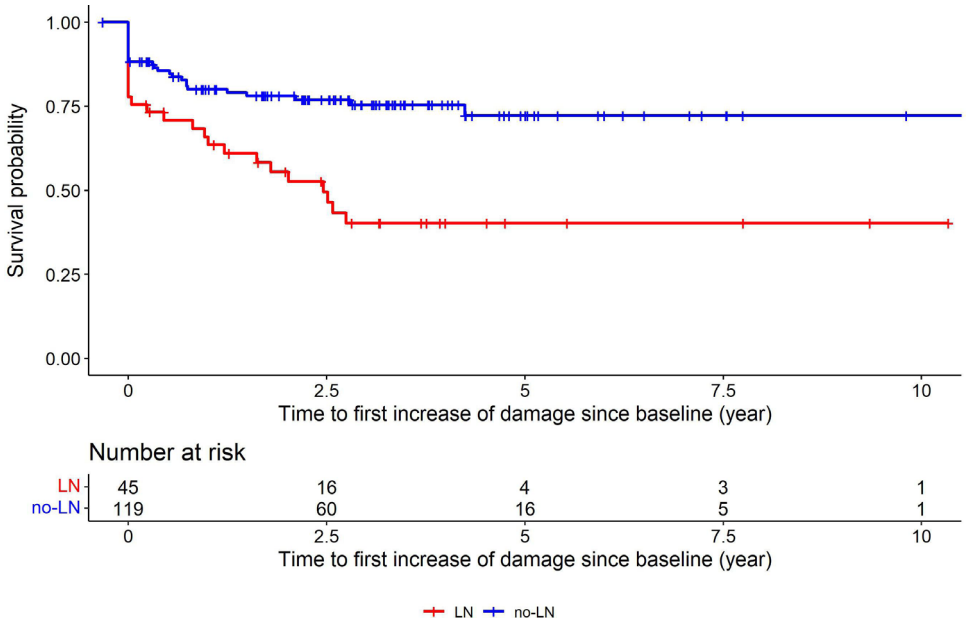


**Figure 2** Time to experiencing additional disease damage in cSLE considering the presence (LN) or absence of kidney involvement (no-LN). Patients with kidney involvement developed damage significantly more rapidly compared with patients who lacked kidney involvement (log-rank p=0.0004). cSLE, childhood-onset SLE; LN, lupus nephritis.

at-risk populations with cSLE, that is, those with LN, non-white race and pre-existing damage, that remain at significantly higher risk of new damage, even if strict T2T goals are achieved.

LLDAS is a composite index that incorporates previously proposed T2T states, such as low-CS[36] and SLEDAI-LD.[7 30] We confirm that the LLDAS is achievable in cSLE.[19 20 37] In our cohort, immunosuppressants were generally well tolerated and did not contribute to patients in low-CS or SLEDAI-LD to not also reaching LLDAS. The reasons for patients with cSLE to not attain LLDAS, despite meeting other T2T states, was the presence of new disease activity.

Studies in adult-onset SLE have shown that achieving LLDAS within the first 6 months post diagnosis significantly lowers the risk of damage accumulation in later stages of the disease[16 17 38] and improves survival.[15 16] We confirm these observations from adult studies that LLDAS achievement is associated with decreased acquisition of further damage. Our results are also congruent with observations by Smith *et al* that LLDAS was associated with reduced acquisition of damage in cSLE.[8]

The LLDAS algorithm, focused on adults with SLE, includes a maximum allowable daily prednisone equivalent dose of 7.5 mg. In children with cSLE, the maximum CS doses acceptable for longer-term use[7] is 0.15 mg/kg/day of prednisone (or its equivalent). This weight-adjusted dose was also used in our analyses and corresponds to 7.5 mg for a 50 kg patient. Hence, consideration should be given to apply a weight-adjusted prednisone dose of 0.15 mg/kg/day with a maximum of 7.5 mg/day when using the LLDAS in cSLE.

Presence of LN is an established risk factor for poor prognosis in both cSLE and adult-onset SLE.[39]

Compared with those without kidney involvement, we report that children with LN were not only significantly less likely to attain any of the T2T-states, including LLDAS, but also required a significantly longer time post diagnosis to do so. As such, 15% fewer patients with LN than versus without LN achieved LLDAS. This difference is much smaller than that reported by Golder *et al* at 46%–86% in adults with LN.[17 18 40] This observed difference in frequency in LLDAS may be due to differences in the study design and the use of cross-sectional statistical approaches. Patients with kidney involvement during the study required an over four times longer time to achieve LLDAS than those without kidney involvement. Indeed, the median time to LLDAS in children with LN was 13.3 months compared with only 3.3 months in those without kidney involvement. The principal reason for not achieving LLDAS in this context was use of higher CS dosage, that is, daily prednisone of >7.5 mg with LN.

In our cohort, the median time to achieving LLDAS at about 7 months was considerably shorter than the time to LLDAS reported by Smith *et al* of 18 months.[3] Besides differences in the racial and ethnic composition of these two paediatric cohorts, differences in medication usage and study design likely accounted for these observed differences. Indeed, the aforementioned publication reported on a cSLE cohort with 30% Asian patients, and 80% of the patients were damage-free at baseline, which compared with 2% and 86% in this US-based cohort.

Considering that LN remained a risk factor of damage progression even after LLDAS achievement, this study showed that an adaptation of the LLDAS might be considered for those with kidney involvement. Such an adaptation could include consideration of renal function,

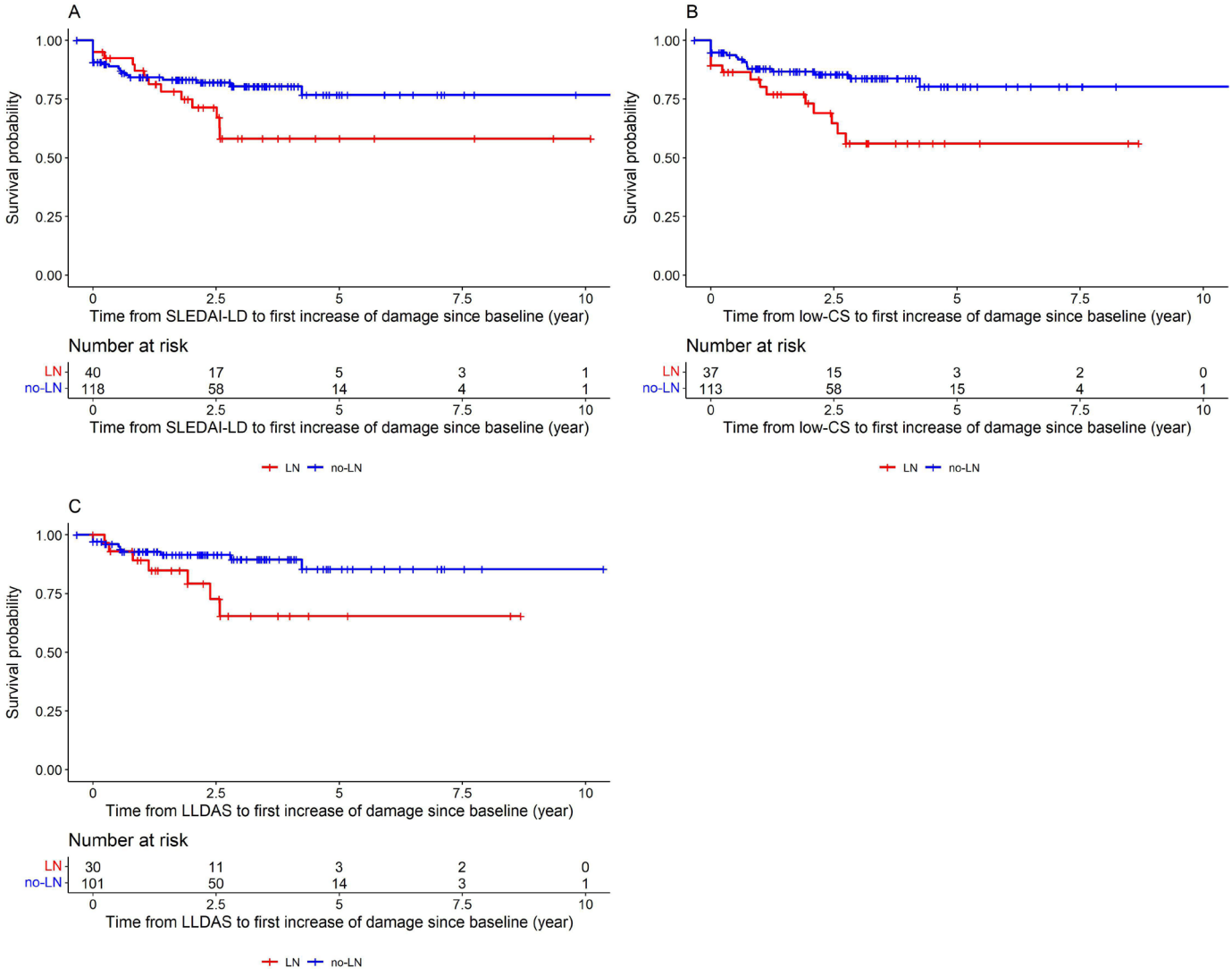


**Figure 3** Time trajectories of acquiring new disease damage after achieving T2T states by kidney involvement (LN or no-LN). (A) There was no significant difference after achieving SLEDAI-LD (p=0.10), whereas patients with cSLE with kidney disease remained at an increased risk of new damage even after achieving CS-low (B, p=0.009) or LLDAS (C, p=0.04) compared with those patients with cSLE who achieved CS-low or LLDAS but lacked kidney involvement. CS, corticosteroid; LLDAS, lupus low disease activity state; LN, lupus nephritis; SLEDAI-LD, SLEDAI score of ≤4; T2T, Treat to target.

presence of hypertension or persistent proteinuria or need of non-immunosuppressant medications to curb proteinuria.[41 42]

On multivariate analysis, age at diagnosis of patients with cSLE was not an important predictor of damage acquisition nor for reaching any of the T2T states, different from pre-existing damage and presence of LN. Conversely, age at diagnosis has been reported to be an important predictor of damage in adult cohorts.[18 40] We hypothesise that this difference is likely due to the relatively short time trajectories in cSLE cohorts and because we purposefully censored follow-up of patients when they reached the age of 18 years.

Like Smith *et al*,[8] we report that non-white patients with cSLE require longer times to reach T2T states, including LLDAS, and hence spend shorter times during the follow-up period in these T2T states.

Besides the presence of kidney involvement, reaching LLDAS in the study cohort of patients with cSLE depended on the presence of pre-existing damage, in our case, acquired around the time of diagnosis, given that the most patients in this study were enrolled by 6 months post diagnosis. Pre-existing damage was not reported as a predictor of LLDAS in other cSLE cohorts[8 20 37] and may be considered a surrogate measure of fulminant disease at cSLE onset.

The T2T measures are not independent from each other, given the variables or measures considered. Thus, it might be expected that achievement of LLDAS is less common than that of CS-low and SLEDA-LD, respectively.

A limitation to our study may be that we evaluated a single-centre cohort with predominantly Caucasian racial background with few Asian or Hispanic patients. The proportion of Asian or Hispanic patients in our

cohort was less than 5%, and no additional detail on the exact racial backgrounds of non-white patients is available. Nonetheless, over 2100 patient visits or 542 PY of follow-up contributed to this study. Indeed, the median time of follow-up was 4 years in this cohort and thus was much longer than those in other cSLE studies with similar objectives.[3 19 20] Further, almost all of our patients were treated with hydroxychloroquine, which may exclude a known effect modifier of damage development.[43]

In conclusion, in this population-based cSLE cohort in the USA, T2T states including LLDAS were achieved in most patients. Presence of LN, pre-existing damage and non-white race were all risk factors not achieving or maintaining these T2T goals and experiencing an increased risk of damage acquisition.

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