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Characterisation and outcomes of different subsets of low disease activity states in patients with systemic lupus erythematosus

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ABSTRACT

Objectives The lupus low disease activity state (LLDAS) allows for certain clinical and/or serological activity of SLE, provided overall disease activity does not exceed predefined cut-offs. This study aimed to evaluate the outcomes of patients who achieved LLDAS with clinical activity, serological activity only or neither clinical nor serological activity.

Methods Patients with SLE enrolled in a prospective multinational cohort from March 2013 to December 2020 who were in LLDAS at least once were included. Visits that fulfilled both LLDAS and Definition of Remission in SLE (DORIS) criteria were excluded.

Results 2099 patients were included, with median follow-up of 3.5 (IQR 1.3–5.8) years. At 6150 visits, patients were in LLDAS but not DORIS criteria; of these 1280 (20.8%) had some clinical activity, 3102 (50.4%) visits had serological activity only and 1768 (28.8%) visits had neither clinical nor serological activity. Multivariable regression analysis showed that compared with non-LLDAS, all three subsets of LLDAS had a protective association with flares in the ensuing 6 months and damage accrual in the ensuing 36 months. LLDAS with no clinical or serological activity had a significantly stronger protective association with severe flares in the ensuing 6 months compared with LLDAS with clinical activity (HR 0.47, 95% CI (0.27 to 0.82), p=0.007).

Conclusions LLDAS without any clinical activity accounted for almost 80% of LLDAS visits. This study confirms that all subsets of LLDAS are associated with reduced flare and damage accrual. However, LLDAS without any clinical or serological activity has the strongest protective association with severe flares.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The lupus low disease activity state (LLDAS) has been shown to be associated with reduced risk of flares, organ damage and death in SLE.

⇒ LLDAS allows serological and certain clinical activities, provided overall disease activity scores do not exceed predefined cut-offs.

WHAT THIS STUDY ADDS

⇒ Examining the presence and absence of clinical and serological activity among patient visits meeting the definition of LLDAS, half of all LLDAS visits had serological activity only, while 20% of LLDAS visits had clinical activity.

⇒ All subsets of LLDAS had a protective association with flare and organ damage accrual, but LLDAS with neither clinical nor serological activity had the strongest protective association with severe flares.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ LLDAS with clinical and/or serological disease activity still confers a protective association with adverse outcomes such as flare and organ damage, but LLDAS with no clinical or serological activity is the most desirable as it has a stronger protective association with severe flares.

⇒ These findings validated the overall definition of LLDAS for use in clinical research and practice in SLE, and revealed that 'not all LLDAS is equal', identifying a subgroup of patients who, despite fulfilling the operational definition of LLDAS, may still require close monitoring and adjustment of treatment to achieve a 'more stringent' LLDAS.

INTRODUCTION

SLE is a chronic autoimmune disease with multi-organ manifestations. Despite emergence of new treatments, irreversible organ damage and mortality in SLE remain unacceptably high.[1 2]

The principle of treat-to-target in SLE was first proposed 9 years ago and has gathered momentum over time, enabled by the definition of therapeutic targets including remission and low disease activity.[3 4]

The lupus low disease activity state (LLDAS), developed by the Asia-Pacific Lupus Collaboration (APLC), is the most widely accepted and used definition of low disease activity in SLE.[5 6] The LLDAS is defined as (1) SLE Disease Activity Index-2K (SLEDAI-2K) ≤4, with no major organ system activity; (2) no new features of activity compared with the previous assessment; (3) Physician Global Assessment (PGA) ≤1 (scale 0–3); (4) current prednisolone (or equivalent) dose ≤7.5 mg/day; with (5) standard doses of immunosuppressive drugs and approved biological agents allowed.[6]

In several real-world cohort studies, the frequency of LLDAS attainment was between 19% and 46% during 1 year of follow-up[7–9] and 87% and 93% after 5 years.[7 8] Numerous studies have shown that LLDAS is associated with reduced flares, damage accrual and death.[5 6 10–13] However, as LLDAS encompasses both clinical and serological activity, the protective effect of subsets of LLDAS with and without clinical and serological activity has not been determined. In the present study, we aimed to characterise patients who achieved LLDAS and examine the outcomes of flare and damage accrual according to different subsets of LLDAS based on serological and clinical activity, compared with not achieving LLDAS.

METHODS

Patients

The APLC cohort is a prospective multinational observational cohort of patients with SLE. Patients in the APLC cohort fulfil either the 1997 American College of Rheumatology (ACR) Modified Classification Criteria[14] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria[15] for SLE. Patients are followed at intervals of between 3 and 6 months. This study included all patients enrolled in the APLC cohort between March 2013 and December 2020 who were aged ≥18 years, had at least two visits and had been in LLDAS at least once during the follow-up period. Visits in which patients were in LLDAS and also met the Definition of Remission in SLE (DORIS) criteria[16] were excluded from the analyses.

Patient and public involvement

Neither patients nor the public were involved in the design or conduct of this study.

Data collection

Patient demographics and SLE-related history were collected at study enrolment. SLE manifestations, SLEDAI-2K,[17] PGA (scale 0–3),[18] medication use including doses of glucocorticoids, hydroxychloroquine, immunosuppressants (IS) and biologics, and disease flares were collected at each visit. The SLICC/ACR Damage Index (SDI)[19] was completed annually. All data were recorded in a standardised electronic case report form.[20]

Determination of low disease activity, remission, flare and damage accrual

LLDAS was defined as described above.[6] Remission was defined according to DORIS, which includes a clinical SLEDAI-2K of 0 (disregarding serology including antidouble-stranded DNA (anti-dsDNA) and complement) with PGA <0.5, allowing a maximum prednisolone dose of 5 mg/day and IS medications.[16]

Disease flare was assessed using the flare definition generated by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial—the SELENA-SLEDAI Flare Index.[21]

Cumulative organ damage was defined according to the SDI, an instrument used to quantify cumulative damage in 12 organ systems. A positive composite damage score (SDI >0) was defined as an indication of presence of organ damage overall and an increase ≥1 in SDI was defined as damage accrual.[19]

Subsets of LLDAS

Patient visits that fulfilled the definition of LLDAS but not the DORIS criteria were categorised into three subsets according to their clinical and serological features: LLDAS with clinical activity according to SLEDAI-2K score regardless of serological status, LLDAS with serological activity only and LLDAS without either clinical or serological activity. The subset of visits in LLDAS without either clinical or serological activity did not fulfil the DORIS criteria due to PGA ≥0.5 or their current prednisolone dose being >5 mg/day.

Statistical analysis

Normally distributed continuous variables were presented as means±SD, skewed continuous variables as medians with IQR and categorical variables as numbers (percentages or proportions). The one-way analysis of variance test was used to compare normally distributed continuous variables, the Kruskal-Wallis test for comparisons of non-normally distributed continuous variables and the χ^2 test was applied to compare categorical variables across groups. Multivariable Cox hazard models for multiple failures were used to determine the association of different LLDAS types with flares at subsequent visits in the next 6 months and the association of different LLDAS types with damage accrual in the next 12, 24 and 36 months following the visit in LLDAS. Age at disease onset, gender, ethnicity, current smoking status, disease duration and prednisolone dose at each visit were also included as covariates in the multivariable Cox hazard models.

All analyses were performed with STATA V.17.0 (StataCorp, College Station, Texas, USA) for Windows and a p value of ≤0.05 was considered statistically significant.

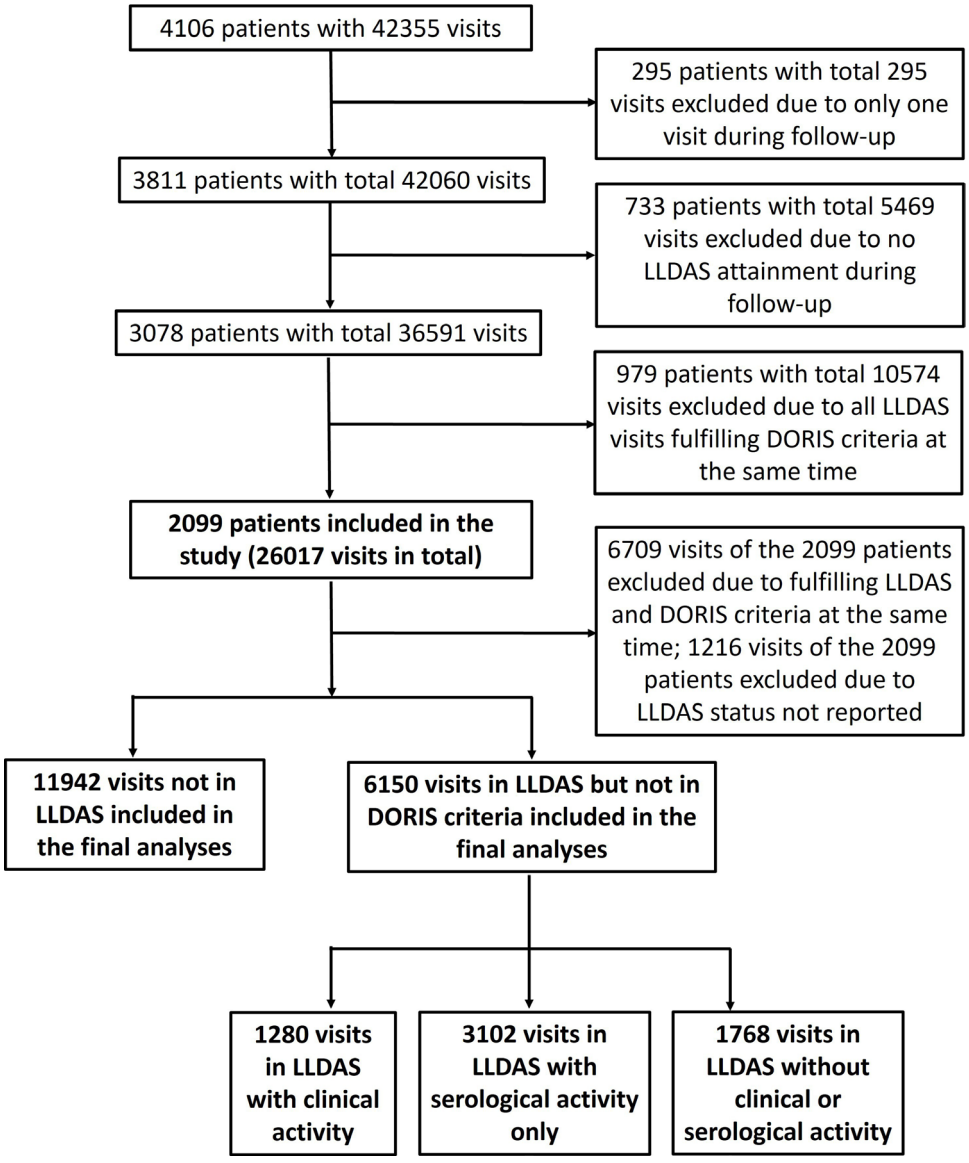

Figure 1 Patient enrolment diagram. DORIS, Definition of Remission in SLE; LLDAS, lupus low disease activity state.

RESULTS

Patient characteristics

Of the 4106 patients with 42 355 visits enrolled in the APLC cohort from March 2013 to March 2021, 295 patients with data recorded from only one visit, 733 patients with no visits in LLDAS and 979 patients whose all LLDAS visits also fulfilled DORIS criteria were excluded, leaving 2099 patients included in this study. Among the total 26 017 visits of the included 2099 patients, 6150 visits which fulfilled the LLDAS criteria but not the DORIS criteria and 11 942 visits which did not fulfil the LLDAS criteria were included in the final analysis (figure 1). The mean age at disease onset of these patients was 31.5±12.9 years; and the cohort was predominantly female (92.3%). The median disease duration at enrolment was 8.0 (3.0–15.0) years, and the median follow-up duration was 3.5 (1.3–5.8) years (table 1).

The time-adjusted mean SLEDAI-2K over the follow-up period was 2.7 (1.3–4.2), and the time-adjusted mean PGA was 0.5 (0.3–0.7). The mean percentage of total follow-up time that patients spent in LLDAS was 57.2%±28.0%; 1021 (57.2%) patients experienced at least one episode of flare, 741/1885 (39.3) patients accrued damage and 32 (1.5%) patients died. In terms of medications, 1828 (87.1%) patients used glucocorticoids with a median prednisolone equivalent dose of 5 (2.5–7.5) mg/day; 1721 (82.0%) patients used antimalarials; 1510 (71.9%) used IS and 72 (3.4%) patients used biologics (table 1).

Characteristics of visits in LLDAS

The 6150 visits in LLDAS but not DORIS criteria included 1280 (20.8%) visits with clinical activity, 3102 (50.4%) visits with serological activity only and 1768 (28.8%) visits without any clinical or serological activity (figure 1). Clinical manifestations included non-vasculitic cutaneous features (38.2%), leucopenia (20.2%), alopecia (18.6%), thrombocytopenia (12.1%), arthritis (10.9%), mucosal ulcers (4.1%) and myositis (0.6%). Thrombocytopenia

Table 1 Characteristics of all included patients with at least one episode of LLDAS

Characteristics	Summary statistics n=2099
Age at enrolment (years), *mean±SD*	40.7±13.5
Age at diagnosis (years), *mean±SD*	31.5±12.9
Disease duration at enrolment (years), *median (IQR)*	8.0 (3.0–15.0)
Follow-up duration (years), *median (IQR)*	3.5 (1.3–5.8)
Total visits per patient during follow-up, *median (IQR)*	10 (5–18)
Female, *n (%)*	1938 (92.3)
Family history of SLE, *n (%)*	152/2069 (7.4)
Asian ethnicity, *n (%)*	1868/2094 (89.2)
Current smoker at enrolment, *n (%)*	113/2083 (5.4)
Tertiary education, *n (%)*	1046/1927 (54.3)
GDP (US$), *n (%)*	
≥50 000	1107 (52.7)
20 000–50 000	285 (13.6)
<20 000	707 (33.7)
Time-adjusted mean SLEDAI-2K during follow-up, *median (IQR)*	2.7 (1.3–4.2)
Time-adjusted mean PGA during follow-up, *median (IQR)*	0.5 (0.3–0.7)
Medication use during follow-up	
Antimalarial use, *n (%)*	1721 (82.0)
Prednisolone use, *n (%)*	1828 (87.1)
Time-adjusted prednisolone dose (mg/day), *median (IQR)*	5 (2.5–7.5)
Immunosuppressant use, *n (%)*	1510 (71.9)
Biological use, *n (%)*	72 (3.4)
Per cent time in LLDAS (%) during follow-up, *mean±SD*	57.2±28.0
Flare at least once during follow-up, *n (%)*	1201 (57.2)
Mild/Moderate flare	1159 (55.2)
Severe flare	549 (26.2)
Number of flares during follow-up, *median (IQR)*	1 (0–3)
Mild/Moderate flare	1 (0–2)
Severe flare	0 (0–1)
Damage present at recruitment, *n (%)*	741/1885 (39.3)
Damage accrual during follow-up, *n (%)*	434/1885 (23.0)
Deaths during follow-up, *n (%)*	32 (1.5)

GDP, Gross Domestic Product per capita; LLDAS, lupus low disease activity state; PGA, Physician Global Assessment; SLEDAI-2K, SLE Disease Activity Index-2K.

was present in 155 visits with a mean platelet count of 72.5±20.4×10^9/L. Serological activity, that is, positive anti-dsDNA and low complement levels, was present both with and without clinical activity. In the LLDAS visits with only serological activity, 31.8% had positive anti-dsDNA antibodies only, 22.1% had low complement only and 46.1% had both. In the LLDAS visits with any clinical activity, 20.1% were anti-dsDNA antibody positive and 15.9% had low complement. The SLEDAI-2K scores of all LLDAS visits without clinical or serological activity were zero; the visits in the other two LLDAS subsets had comparable mean SLEDAI-2K scores. Regarding treatment, the mean daily prednisolone doses for all three subsets of LLDAS were all <5 mg. Visits with clinical activity (3.4±2.6 mg/day) had a lower dose than those without (4.3±2.7 mg/day and 4.4±2.8 mg/day, with and without serological activity, respectively). Meanwhile, LLDAS with only serological activity had a higher percentage of antimalarial and IS use than the other subsets (table 2).

Flare and damage accrual according to LLDAS subset

Compared with the visits which were in LLDAS, a significantly higher proportion of the visits which were not in LLDAS had flare/s at the next visit (16.1% vs 12.5%, p<0.001) as well as in the subsequent 6 months (24.1% vs 16.6%, p<0.001) (online supplemental table

Table 2 Characteristics of all visits (n=6150) in LLDAS but not in DORIS criteria

Characteristics	Visits in LLDAS with clinical activity (subset 1) n=1280	Visits in LLDAS with serological activity only (subset 2) n=3102	Visits in LLDAS without serological or clinical activity (subset 3) n=1768	P value
Clinical disease activity according to SLEDAI-2K, *n (%)*				
Non-vasculitis cutaneous features	489 (38.2)	–	–	–
Leucopenia	259 (20.2)	–	–	–
Alopecia	238 (18.6)	–	–	–
Thrombocytopenia	155 (12.1)	–	–	–
Arthritis	140 (10.9)	–	–	–
Mucosal ulcers	53 (4.1)	–	–	–
Myositis	7 (0.6)		–	–
Serological disease activity according to SLEDAI-2K, *n (%)*				
Positive anti-dsDNA antibody only	257 (20.1)*	987 (31.8)	–	<0.001
Low complement level only	204 (15.9)*	686 (22.1)	–	<0.001
Positive anti-dsDNA and low complement	0 (0)*	1429 (46.1)	–	<0.001
Medication use				
Prednisolone dose (mg/day), *mean±SD*	3.4±2.6*†	4.3±2.7	4.4±2.8	<0.001
Antimalarial use, *n (%)*	880 (68.8)*†	2381 (76.8)‡	1141 (64.5)	<0.001
Immunosuppressant use, *n (%)*	660 (51.6)*†	1899 (61.2)‡	1021 (57.8)	<0.001
Biological use, *n (%)*	14 (1.1)	48 (1.6)	18 (1.0)	0.223
SLEDAI-2K score, *mean±SD*	2.7±1.1*†	2.9±1.0‡	0	<0.001
PGA, *mean±SD*	0.4±0.3*†	0.6±0.3‡	0.5±0.3	<0.001

*P<0.05 when subset 1 LLDAS versus subset 2 LLDAS.
†P<0.05 when subset 1 LLDAS versus subset 3 LLDAS.
‡P<0.05 when subset 2 LLDAS versus subset 3 LLDAS.
DORIS, the Definitions of Remission in SLE; ds, double-stranded; LLDAS, lupus low disease activity state; PGA, Physician Global Assessment; SLEDAI-2K, SLE Disease Activity Index-2K.

Table 3 Association of different LLDAS subsets with flare in the next 6 months by multivariable Cox regression analyses*

Visits with different LLDAS status	Any flare† in the next 6 months		Any flare† in the next 6 months		Severe flare in the next 6 months		Severe flare in the next 6 months	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Non-LLDAS	*Reference*	–	–	–	*Reference*	–	–	–
LLDAS with clinical activity	0.57 (0.45 to 0.72)	<0.001	*Reference*	–	0.40 (0.27 to 0.61)	<0.001	*Reference*	–
LLDAS with serological activity only	0.50 (0.43 to 0.58)	<0.001	0.83 (0.66 to 1.06)	0.141	0.33 (0.26 to 0.42)	<0.001	0.75 (0.48 to 1.18)	0.211
LLDAS without any clinical or serological activity	0.52 (0.42 to 0.63)	<0.001	0.83 (0.64 to 1.07)	0.153	0.21 (0.14 to 0.33)	<0.001	0.47 (0.27 to 0.82)	0.007

*Adjusted by age at diagnosis, gender, ethnicity, current smoker, disease duration and prednisolone dose at visit.
†Any flares include mind/moderate flares and severe flares.
LLDAS, lupus low disease activity state.

1). Comparison among the three subsets of LLDAS visits showed no significant difference in rates of mild/moderate flare(s). However, a lower proportion of LLDAS visits with neither clinical nor serological activity had subsequent severe flare(s) at the next visit (p=0.038) or in the next 6 months (p=0.022) than the visits with the other subsets of LLDAS (online supplemental table 1).

Similarly, a significantly higher proportion of non-LLDAS visits were followed by subsequent damage accrual over 12, 24 and 36 months compared with the visits in LLDAS (9.6% vs 7.3% at 12 months; 14.6% vs 10.1% at 24 months and 17.6% vs 12.0% at 36 months, all p<0.001). However, no significant difference in subsequent damage accrual was observed among the three subsets of LLDAS (online supplemental table 1).

Association of different subsets of LLDAS with subsequent flare

The multivariable hazard model showed that compared with visits that were not in LLDAS, all three subsets of LLDAS visits had an independently protective association with flares at the immediate subsequent visit and for visits occurring within the next 6 months after LLDAS attainment, including both mild/moderate flares and severe flares. Furthermore, compared with LLDAS with clinical activity, LLDAS without clinical activity did not have additional protective associations in terms of flare. However, for severe flares at both the next visit and over the ensuing 6 months, LLDAS without any clinical or serological activity had significantly stronger protective association compared with LLDAS with clinical features (next visit HR 0.48, 95% CI (0.28 to 0.84), p=0.010; next 6 months HR 0.47, 95% CI (0.27 to 0.82), p=0.007) (table 3 and online supplemental table 2).

Association of different subsets of LLDAS with subsequent damage accrual

In the multivariable hazard models for damage accrual, all three subsets of LLDAS had significantly protective associations with damage accrual over the subsequent 12, 24 and 36 months when compared with non-LLDAS visits. The three LLDAS subsets did not significantly differ regarding association with damage accrual over the

Table 4 Association of different LLDAS subsets with damage accrual in the next 12 months by multivariable Cox regression analysis*

Visits with different LLDAS status	Damage accrual in the next 12 months		Damage accrual in the next 12 months	
	HR (95% CI)	P value	HR (95% CI)	P value
Non-LLDAS	*Reference*	–	–	–
LLDAS with clinical activity	0.64 (0.46 to 0.89)	0.008	*Reference*	–
LLDAS with serological activity only	0.61 (0.48 to 0.79)	<0.001	0.90 (0.63 to 1.29)	0.577
LLDAS without any clinical or serological activity	0.66 (0.50 to 0.89)	0.006	0.89 (0.62 to 1.29)	0.548

*Adjusted by age at diagnosis, gender, ethnicity, current smoker, disease duration and prednisolone dose at visit.
LLDAS, lupus low disease activity state.

ensuing 12, 24 and 36 months (table 4, online supplemental tables 3,4).

DISCUSSION

Attainment of low disease activity in SLE is included in the updated EULAR recommendations for SLE as a treatment target.[22] LLDAS is the most widely accepted and validated[23–27] low disease activity end point for SLE. According to the definition of LLDAS, major organ system activity such as renal, central nervous system, cardiopulmonary, vasculitis, fever, haemolytic anaemia or gastrointestinal activity is excluded. However, patients in LLDAS can exhibit clinical activity as long as the clinical feature is not new, and the other criteria are fulfilled including a maximum SLEDAI-2K score of 4.[5] Therefore, patients in LLDAS have some degree of heterogeneity, but differences in outcome between different subsets within LLDAS have not been well studied.

We examined patients who achieved LLDAS but not DORIS criteria at least once and categorised subsets of LLDAS with and without clinical and serological activity. We found that 20.8% of visits that met LLDAS criteria had active clinical manifestations; among them, mucocutaneous features, including rash, alopecia and mucosal ulcers, were the most common manifestations accounting for 60.9% of all clinical manifestations. Other less common manifestations included leucopenia, thrombocytopenia, arthritis and myositis.

Half of the visits in LLDAS had serological activity only, and 46.1% of these had both positive anti-dsDNA and low complement. Nearly a third of visits in LLDAS had neither serological nor clinical activity. In our study, visits that fulfilled the DORIS criteria simultaneously were excluded, and thus for this subset of LLDAS, DORIS criteria were not fulfilled due to a higher prednisolone dose or a higher PGA than the DORIS cut-off values.

Flares, which occur very commonly during the SLE disease course, are associated with a significant clinical burden, as well as organ damage accrual.[28 29] Therefore, flare prevention is imperative to effective management of SLE. The results of the present study showed that compared with the visits that did not meet LLDAS criteria, flares in the ensuing 6 months were significantly less frequent following visits that attained LLDAS. The Cox hazard model showed that all three subsets of LLDAS were protectively associated with subsequent flares, compared with non-LLDAS visits, after adjustment for covariates. Many studies have demonstrated the protective association of LLDAS with flares,[5 6 10–12] but this is the first study to confirm this association among three subsets of LLDAS according to clinical and serological activity.

With LLDAS with clinical activity used as reference, the other two subsets of LLDAS did not show additional protection associations for subsequent flares overall. However, LLDAS without any clinical or serological activity showed a significantly greater protective association with severe flares compared with LLDAS with clinical features, highlighting the need for close monitoring of patients in LLDAS who still have some clinical activity.

Organ damage accrual, including cardiovascular and cerebrovascular complications, has become the leading cause of death in patients with SLE.[30–32] Therefore, the ultimate treatment goal of SLE should be prevention of damage accrual.[4] LLDAS attainment has been found to be associated with reduced organ damage accrual in several studies[5 6 25–27] and the present study confirmed that all subsets of LLDAS have equally protective associations with damage accrual in the ensuing 36 months. This is reassuring regarding the use of LLDAS as a treat to target end point in clinical practice, and also in extrapolating the value of different rates of LLDAS attainment in clinical trials, which typically have a duration of only 1 year.[33 34]

There are some limitations in this study. First, to remove the influence of DORIS criteria on outcomes, including the subsequent flares and damage accrual, 17 283 visits that fulfilled both LLDAS and DORIS criteria simultaneously were excluded from the analysis to avoid the influence of DORIS criteria attainment for the subsequent flare and damage accrual. This exclusion may have some effect on the overall magnitude of associations determined in our analyses, as most studies of LLDAS included patients in LLDAS who also meet the effectively concentric definition of remission. Regarding analyses for damage accrual, SDI assessments were performed annually and all the reviews with SDI assessments were included in our analyses, meaning no damage accrual data were missed. Second, damage accrual sometimes occurs after many years of disease, and the median follow-up in the present study was 3.5 years, which may be insufficient for evaluating damage accrual, especially in relation to possible differences among different subsets of LLDAS. Third, we did not further differentiate the visits of LLDAS with clinical activity (subset 1) by their serological status because we aimed to answer the question of whether having clinical activity in LLDAS versus serological activity alone make a difference to the outcomes. Fourth, we did not include mortality as an outcome in this study, as there was not a sufficient number of deaths to power a multivariable analysis for the relationship between different subsets of LLDAS and mortality, due to a relatively limited follow-up duration (median 3.5 IQR 1.3–5.8 years). Finally, in a prospective cohort study, we are limited to inferences regarding associations rather than making conclusions regarding causal effects.

In conclusion, there are three different LLDAS presentations according to the presence of clinical and serological characteristics. In this study, while LLDAS without clinical activity accounted for 80% of LLDAS visits, all subsets of LLDAS had a significant protective association with flares and damage accrual. However, LLDAS without any clinical or serological activity had a stronger protective association with subsequent severe flares. These findings further validate the overall definition of LLDAS for use in clinical research and practice in SLE.

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REFERENCES

1 Lee YH, Choi SJ, Ji JD, *et al*. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus (Los Angel)* 2016;25:727–34.
2 Mu L, Hao Y, Fan Y, *et al*. Mortality and prognostic factors in Chinese patients with systemic lupus erythematosus. *Lupus (Los Angel)* 2018;27:1742–52.
3 Franklyn K, Hoi A, Nikpour M, *et al*. The need to define treatment goals for systemic lupus erythematosus. *Nat Rev Rheumatol* 2014;10:567–71.
4 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.
5 Franklyn K, Lau CS, Navarra SV, *et al*. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
6 Golder V, Kandane-Rathnayake R, Huq M, *et al*. Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. *Lancet Rheumatol* 2019;1:e95–102.
7 Babaoğlu H, Li J, Goldman D, *et al*. Time to Lupus Low Disease Activity State in the Hopkins Lupus Cohort: Role of African American Ethnicity. *Arthritis Care & Research* 2020;72:225–32.
8 Gao D, Hao Y, Mu L, *et al*. Frequencies and predictors of the Lupus Low Disease Activity State and remission in treatment-naïve patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2020;59:3400–7.
9 Kikuchi J, Hanaoka H, Saito S, *et al*. Lupus low disease activity state within 12 months is associated with favourable outcomes in severely active systemic lupus erythematosus. *Rheumatology (Oxford)* 2022;61:3777–91.
10 Zen M, Saccon F, Gatto M, *et al*. Prevalence and predictors of flare after immunosuppressant discontinuation in patients with systemic lupus erythematosus in remission. *Rheumatology (Oxford)* 2020;59:1591–8.
11 Hao Y, Oon S, Ji L, *et al*. Determinants and protective associations of the lupus low disease activity state in a prospective Chinese cohort. *Clin Rheumatol* 2022;41:357–66.
12 Hao Y, Ji L, Gao D, *et al*. Flare rates and factors determining flare occurrence in patients with systemic lupus erythematosus who achieved low disease activity or remission: results from a prospective cohort study. *Lupus Sci Med* 2022;9:e000553.
13 Kandane-Rathnayake R, Golder V, Louthrenoo W, *et al*. Lupus low disease activity state and remission and risk of mortality in patients with systemic lupus erythematosus: a prospective, multinational, longitudinal cohort study. *Lancet Rheumatol* 2022;4:e822–30.
14 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
15 Petri M, Orbai A-M, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
16 van Vollenhoven RF, Bertsias G, Doria A, *et al*. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2021;8:e000538.
17 Ibañez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. *J Rheumatol* 2005;32:824–7.
18 Petri M, Hellmann D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinic setting. *J Rheumatol* 1992;19:53–9.
19 Gladman DD, Goldsmith CH, Urowitz MB, *et al*. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. *J Rheumatol* 2000;27:373–6.
20 Kandane-Rathnayake R, Golder V, Louthrenoo W, *et al*. Development of the Asia Pacific Lupus Collaboration cohort. *Int J Rheum Dis* 2019;22:425–33.
21 Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. *Lupus (Los Angel)* 1999;8:685–91.
22 Fanouriakis A, Kostopoulou M, Andersen J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024;83:15–29.
23 Golder V, Tsang-A-Sjoe MWP. Treatment targets in SLE: remission and low disease activity state. *Rheumatology (Oxford)* 2020;59:v19–28.
24 Tsang-A-Sjoe MWP, Bultink IEM, Heslinga M, *et al*. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology (Oxford)* 2017;56:121–8.
25 Zen M, Iaccarino L, Gatto M, *et al*. Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;77:104–10.
26 Petri M, Magder LS. Comparison of Remission and Lupus Low Disease Activity State in Damage Prevention in a United States Systemic Lupus Erythematosus Cohort. *Arthritis Rheumatol* 2018;70:1790–5.
27 Sharma C, Raymond W, Eilertsen G, *et al*. Association of Achieving Lupus Low Disease Activity State Fifty Percent of the Time With Both Reduced Damage Accrual and Mortality in Patients With Systemic Lupus Erythematosus. *Arthritis Care & Research* 2020;72:447–51.
28 Koutsonikoli A, Trachana M, Heidich A-B, *et al*. Dissecting the damage in Northern Greek patients with childhood-onset systemic lupus erythematosus: a retrospective cohort study. *Rheumatol Int* 2015;35:1225–32.
29 Ugarte-Gil MF, Acevedo-Vásquez E, Alarcón GS, *et al*. The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort. *Ann Rheum Dis* 2015;74:1019–23.
30 Thomas G, Mancini J, Jourde-Chiche N, *et al*. Mortality Associated With Systemic Lupus Erythematosus in France Assessed by Multiple-Cause-of-Death Analysis. *Arthritis & Rheumatology* 2014;66:2503–11.
31 Rees F, Doherty M, Grainge MJ, *et al*. Mortality in systemic lupus erythematosus in the United Kingdom 1999-2012. *Rheumatology (Oxford)* 2016;55:854–60.
32 Elfving P, Puolakka K, Kautiainen H, *et al*. Mortality and causes of death among incident cases of systemic lupus erythematosus in Finland 2000-2008. *Lupus (Los Angel)* 2014;23:1430–4.
33 Morand E, Pike M, Merrill JT, *et al*. Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheumatol* 2023;75:242–52.
34 Morand EF, Abreu G, Furie RA, *et al*. Lupus low disease activity state attainment in the phase 3 TULIP trials of anifrolumab in active systemic lupus erythematosus. *Ann Rheum Dis* 2023;82:639–45.