Arthritis Australia 2024 National Research Program

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Defining the Lupus Low Disease Activity State (LLDAS) using the British Isles Lupus Assessment Group Index (BILAG-2004): a prospective cohort study.

Research Team

Luigi Zolio[1,2,3], Dylan Hansen[3], Carmen San José Méndez[4], Gullu Sandal Uzun[5], Shereen Oon[1,3], Mandana Nikpour[1,3,6], Anisur Rahman[2], David Isenberg[2].

1. University of Melbourne at St Vincent's Hospital, Melbourne VIC, Australia
2. Department of Aging, Rheumatology and Regenerative Medicine, University College London, London, UK
3. Department of Rheumatology, St Vincent's Hospital Melbourne, Melbourne VIC, Australia
4. Hospital Universitario de A Coruña, A Coruña, Spain.
5. Department of Rheumatology, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye
6. University of Sydney, Camperdown NSW, Australia

PhD Candidate:

Dr Luigi Zolio, MBBS(Hons), BMedSc(Hons), FRACP
PhD Candidate
Department of Medicine, University of Melbourne at St Vincent's Hospital
A: Level 3 Daly Wing, 41 Victoria Parade, Fitzroy VIC 3145, Australia
E: luigi.zolio@student.unimelb.edu.au
T: +61 (3) 9231 2211

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Background and Aims of the Project

Systemic Lupus Erythematosus (SLE) is a heterogenous multisystem disease where damage is accrued over time due to both disease and treatment burden (1). Having had a limited repertoire of treatments for the last fifty years, partly due to lack of well-defined and validated clinical trial treatment endpoints, we are now on the cusp of having several new treatment options for this complex disease. This has been evidenced by the approvals of belimumab and anifrolumab in the last fifteen years (2, 3). In this context, there has been growing interest in adopting a 'Treat to Target' strategy in SLE, akin to the one that transformed the outlook for treatment of rheumatoid arthritis (4).

The Lupus Low Disease Activity State (LLDAS) was defined by the Asia Pacific Lupus Collaboration (APLC) and is now the most-commonly used definition of low disease activity in clinical practice (5). It is proposed as a treatment target, although prospective Treat to Target clinical trials demonstrating that attainment of LLDAS portends better outcomes are still pending. LLDAS is defined as a list of five components including a disease activity measure namely the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (6). Briefly, LLDAS is defined as (i) SLEDAI-2K ≤ 4; (ii) no new features of disease activity; (iii) Physician Global Assessment (PGA) ≤ 1 (on scale from 0 to 3 where 3 is maximum disease activity) (7); (iv) prednisolone ≤ 7.5 mg daily and (v) antimalarials and immunosuppressives allowed (5).

SLEDAI-2K is a feasible tool for use in clinical practice due to its relative brevity and ease of calculating a final score. However, it has some critical limitations that limit its use in clinical practice and may negatively influence clinical trial results: it does not capture worsening or improvement in individual lupus manifestations, and it lacks some important organ manifestations (8). The British Isles Lupus Assessment Group (BILAG) Index was designed to capture severity of disease activity and includes more organ systems than the SLEDAI-2K (9). The BILAG Index is also a very commonly used measure of disease activity. Some have criticised it for the length of time required to complete and calculate a final score in some patients (8), and this has led to the creation of a simplified version to aid its implementation in practice, the Easy-BILAG (10). The Easy-BILAG has been previously validated to have similar or potentially superior accuracy compared to the original BILAG Index in a clinical practice exercise (10). Whilst a SLEDAI-2K measurement cannot be converted to a BILAG-2004 measurement, BILAG-2004 can be used to calculate an equivalent SLEDAI score. So, in a cohort setting where the BILAG is routinely measured, one can translate the BILAG Index, or find a BILAG *equivalent* of the SLEDAI-based LLDAS definition without repeating each step of the LLDAS consensus development.

In this proposed project we aimed to define a BILAG Index version of LLDAS to allow the LLDAS to be applied as a potential treatment target in settings where the BILAG Index is the most commonly used instrument to measure disease activity. We also aimed to explore whether the BILAG-LLDAS is able to predict major outcomes in an equivalent, inferior or superior manner to the original SLEDAI-based LLDAS definition. Finally, we aimed to demonstrate face-validity of the Easy-BILAG Index for assessing BILAG-LLDAS in a case-based study.

Methodology

Patients

This study utilised demographic, clinical and laboratory data collected as part of routine clinical care from SLE patients $\geq$18 years old receiving care from UCLH and enrolled in a prospective observational cohort study (1978-present). All patients enrolled met the 1997 American College of Rheumatology (ACR) SLE classification criteria (11). BILAG-2004 assessments have been collected from patients

enrolled in the cohort study from January 2011 to the present. Patients' visit frequency varied according to clinical need.

Ethics approval

No formal ethical approval was deemed required for the collection and use of deidentified patient data, according to standard practice at the institution. This is compliant with Data Protection laws in the United Kingdom (12). A low-risk ethics approval and data collaboration and data sharing agreement was obtained from St Vincent's Hospital Melbourne for the sharing of deidentified patient data, for the purpose of statistical analysis (Reference:111066).

Inclusion criteria

Patients were included if they had at least two visits with BILAG-2004 assessments, treatment and laboratory (haematological, biochemical and serological) data available. All eligible visit data from the prospective observational cohort study from January 2011-September 2024 were included.

Exclusion criteria

Patients and/or patient visits without BILAG-2004 assessments or missing prednisolone or serologic marker data were excluded.

BILAG-LLDAS definition

We translated the SLEDAI-2K-based criteria of the LLDAS definition to define the proposed BILAG-2004 criteria for BILAG-LLDAS. Serological disease activity according to low complement levels (C3 and/or C4) and raised anti-double-stranded DNA antibodies was allowed, as these variables are not included in BILAG-2004. The criterion for treatments for BILAG-LLDAS was identical to the original LLDAS definition listed above (SLEDAI-LLDAS). The PGA criterion was omitted, due to lack of prospectively collected retrospective data from the cohort and because we hypothesised that it would not be necessary for BILAG-LLDAS. We used the standard definition of SLEDAI-LLDAS but without the PGA criterion.

Variables

Baseline demographic data including age, sex, years of education, smoking status at enrolment, ethnicity, disease duration at first included visit (time-zero) were documented.

BILAG-2004 data were obtained from the UCLH i-BLIPS® database (13). Treatment data were also collected at every visit, including prednisolone, hydroxychloroquine, immunosuppressants (mycophenolate, azathioprine, methotrexate, leflunomide, ciclosporin, tacrolimus) and biologics (rituximab and belimumab). By applying glossary definitions of SLEDAI-2K and BILAG-2004 and using laboratory data, we translated BILAG-2004 assessment to SLEDAI-2K scores at each visit. Using the above data, SLEDAI-LLDAS and BILAG-LLDAS status were ascertained for each visit of each patient.

The primary flare outcome for the analysis was new BILAG A or B flare. A range of secondary flare outcomes using both BILAG-2004 and SLEDAI-2K, including assessment over continuous periods in LLDAS states were also determined and tabulated.

Organ damage was documented using the SLICC/ACR Damage Index (SDI) (14) from retrospective patient file reviews at time points including years 1,5,10,15,20 and 25 post-initial diagnosis. Mortality and date of death were documented, from which disease duration and follow-up duration at time of death were calculated. We included all deaths occurring up to 12 months after the last visit in the analysis.

Project to determine relevance of PGA score to BILAG-LLDAS

We conducted a parallel prospective study between November 2024 and May 2025 to test our hypothesis that PGA score would not affect BILAG-LLDAS assessment. PGA scores were documented alongside BILAG-2004 assessments as part of routine clinical care, according to the PGA International Standardisation Consensus in SLE (PISCO) study (7). SLEDAI-LLDAS and BILAG-LLDAS status were derived from BILAG-2004 scores and laboratory results, and we assessed whether that would have changed dependent on the PGA score.

Statistical analysis

Data were analysed using STATA Version 18 (StataCorp, Texas) (15). We defined statistical significance according to p-value $\leq$0.05 for all analyses.

Baseline demographic and individual visit clinical and laboratory data were analysed using descriptive statistics, reporting measures of central tendency for continuous variables, and proportions and percentages for categorical data. We compared categories of LLDAS using the chi-squared test for binary or categorical variables, or ANOVA for continuous variables.

BILAG-LLDAS and SLEDAI-LLDAS status were assessed in the regression models according to: $\geq$50% follow-up time in LLDAS (occurrence of flare, organ damage or mortality during follow-up), and continuous 6-, 12-, 18- and 24-month periods in LLDAS (flare at next visit).

Hazard of flare (new flare) values were calculated according to attainment of each LLDAS variable, using multiple failures (Anderson-Gill) Cox regression models. Hazard of organ damage (increase in SDI at a visit) were calculated according to each respective LLDAS variable in single-failure Cox regression models stratified for presence of prior damage at time-zero, since recurrent damage events were rare in the patient group. Hazard of mortality as predicted by each respective LLDAS definition was calculated using multivariable single-failure Cox-regression models, adjusted for age at diagnosis, gender and disease duration as a time-varying covariate. Damage and mortality regression analyses were limited to patients with at least 12 months of follow-up. The proportional hazards assumption was verified for all regression models.

Regression model coefficients (hazard ratios), 95% confidence interval and p-values were tabulated. Regression models for BILAG- and SLEDAI-based LLDAS definitions were compared using the Aikake Information Criterion (AIC) and Bayesian Information Criterion, with smaller AIC and BIC values indicative of better model fit.

The unadjusted probability of survival from first flare (for each above definition), first organ damage accrual, or mortality was calculated using Kaplan-Meier analysis for each variable. P-values were calculated using the log-rank test.

Changes to the project

Upon further discussion within the project team, it was assessed that Aim 3 (Easy-BILAG Case-based Exercise) was similar to prior work already published using Easy-BILAG and was not necessary for validation of the BILAG-LLDAS definition. Therefore, further work on Aim 3 has been deferred.

However, the construction of the SLE cohort patient database as defined for this project inspired further research projects and international collaborations. These collaborations are currently being prepared for presentation and publication (see ‘Research Outputs’).

Project outcomes

We included 604 patients and over 10 000 patient visits in the analysis.

We firstly identified that the states of SLEDAI-LLDAS and BILAG-LLDAS overlapped in the majority of cases. BILAG-LLDAS was a slightly less infrequent clinical state. We identified in our sensitivity analysis that a PGA criterion did not add further discriminative value to the BILAG-LLDAS definition, while it altered the SLEDAI-LLDAS state ascertainment in a small number of visits.

SLEDAI- and BILAG-LLDAS were protective from flare across all flare definitions assessed. AIC and BIC values were lower for BILAG-LLDAS models for most flare definitions, indicative that BILAG-LLDAS is potentially a more discriminative definition. Hazard ratios for BILAG-LLDAS were lower than or equivalent to SLEDAI-LLDAS hazard ratios for flare across most flare definitions.

We found a non-statistically significant trend toward protection from organ damage for patients who attained LLDAS for ≥50% of follow-up time. We postulate this to be due to limited measurements of SDI during the follow-up period.

We found that both BILAG and SLEDAI-LLDAS status attainment for ≥50% of follow-up time was protective from mortality, in keeping with prior studies.

Impact and translation

The translated BILAG-LLDAS definition demonstrates similar predictiveness to the original SLEDAI-2K based definition for predicting future flares, organ damage and mortality. We found that BILAG-LLDAS obviates the need for a PGA criterion, which would significantly simplify its future implementation in clinical practice and research. Meanwhile PGA added discriminative value to SLEDAI-LLDAS. Furthermore, BILAG-2004 and it enables clinicians to document active disease manifestations not captured by SLEDAI-2K, providing a more accurate depiction of the state of disease activity in a given visit, and between visits. BILAG-LLDAS may become a more feasible way to use a low disease activity definition as part of a treat-to-target strategy in clinical practice and research.

Research outputs

A manuscript is currently under preparation for submission for publication.

Other research outputs completed or contributed to by the PhD Candidate during the Award period:

1. **Zolio L**, Cohen H, Isenberg D. Challenges of anticoagulation in patients with systemic lupus erythematosus. Expert Opin Pharmacother. 2025 May;26(7):849-862. doi: 10.1080/14656566.2025.2491509. Epub 2025 May 7.
2. [Submitted] Kandane-Rathnayake R*, **Zolio L*,** Choi J et al. Predictors of Organ Damage in systemic lupus erythematosus. Rheumatology (Oxford).
   *co-first authorship
3. [Submitted] **Zolio L*, Hao YJ,** Kandane-Rathnayake R et al. Prevalence and predictive correlates of arthritis and joint damage in patients with systemic lupus erythematosus. Rheumatology (Oxford)
   *co-first authorship
4. **Zolio L**, Hansen D, Kandane-Rathnayake et al. Determinants of the Physician's Global Assessment Score in systemic lupus erythematosus patients in low disease activity. Accepted for Oral Presentation at Asia-Pacific Lupus Collaboration Investigators Meeting, Fukuoka, Japan. 3rd Sep 2025.

5. Piunno S, Ortolan A, **Zolio L**, D'Agostino MA, Rahman A, Isenberg D. Serologically active clinically quiescent systemic lupus erythematosus: a prospective study on the role of anti-dsDNA IgG and complement. Accepted for Poster Presentation, Congresso Annnuale della Societa Italiana di Reumatologia (SIR). Rimini, Italy 26-29 Nov 2025.

Other manuscripts in preparation for publication

1. **Zolio L**, Hansen D, Kandane-Rathnayake et al. Determinants of the Physician's Global Assessment Score in systemic lupus erythematosus patients in low disease activity.
2. **Zolio L**, Saracino A, Oon S, Nikpour M, D Isenberg, Rahman A. Prevalence and correlates of mucocutaneous disease activity and organ damage in patients with systemic lupus erythematosus.

Use of funding

The funding was used as PhD stipend support for Dr Zolio, as outlined in the original project grant application. The funding supported Dr Zolio's relocation and living costs while residing in the UK.

Other progress

In recognition of the aims and scope of Dr Zolio's work, his Master of Medicine (Research) was converted to a Doctor of Philosophy (PhD) at University of Melbourne, admitted as a Confirmed Candidate in September 2024.

Dr Zolio completed a 12-month clinical and research Fellowship at University College London and University College London Hospital. Additional to the above research project, he consulted in the weekly Autoimmune Rheumatic Diseases (SLE) clinic, Osteoporosis Clinic, General Rheumatology Clinic and worked in the inpatient Rheumatology service at UCLH, broadening his clinical experience. This clinical experience provided significant clinical context to his SLE research, and data collection was facilitated by his clinical work.

Formal Training

University of Melbourne Coursework Completed:

1. Biostatistics 1, Semester 1 2024. First Class Honours
2. Epidemiology 1, Semester 1 2024. First Class honours
3. Regression Methods in Health Research, Semester 2 2024. First Class Honours
4. Survival Analysis & Regression for Rates, Semester 2 2024. First Class Honours

Introduction to STATA 1 and 2, Murdoch Children's Research Institute, Melbourne VIC, Australia. March and May 2024.

Fellowship of Royal Australasian College of Physicians (FRACP), December 2024

Other Professional Development

Delegate, European Alliance of Associations for Rheumatology (EULAR) Congress, Barcelona, June 2025

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REFERENCES

1. Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, et al. Systemic lupus erythematosus. Nature Reviews Disease Primers. 2016;2(1):16039.
2. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. New England Journal of Medicine. 2020;382(3):211-21.
3. Parodis I, Lindblom J, Levy RA, Zen M, Cetrez N, Gomez A, et al. Attainment of remission and low disease activity after treatment with belimumab in patients with systemic lupus erythematosus: a post-hoc analysis of pooled data from five randomised clinical trials. Lancet Rheumatol. 2024;6(11):e751-e61.
4. Piga M, Parodis I, Touma Z, Legge A, Ugarte-Gil MF, Hmamouchi I, et al. Framework for implementing treat-to-target in systemic lupus erythematosus routine clinical care: consensus statements from an international task force. Autoimmunity Reviews. 2025;24(5):103773.
5. Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2016;75(9):1615-21.
6. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. The Journal of Rheumatology. 2002;29(2):288-91.
7. Piga M, Chessa E, Morand E, Ugarte-Gil M, Tektonidou M, Vollenhoven R, et al. Physician Global Assessment International Standardisation COnsensus in Systemic Lupus Erythematosus: the PISCOS study. The Lancet Rheumatology. 2022;4.
8. Ohmura K. Which is the best SLE activity index for clinical trials? Modern Rheumatology. 2021;31(1):20-8.
9. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology. 2005;44(7):902-6.
10. Carter LM, Gordon C, Yee C-S, Bruce I, Isenberg D, Skeoch S, et al. Easy-BILAG: a new tool for simplified recording of SLE disease activity using BILAG-2004 index. Rheumatology. 2022;61(10):4006-15.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
12. Information Commissioner's Office. Introduction to anonymisation [internet]. Wilmslow (UK): Information Commissioner's Office; 28 March 2025 [cited 2025 Aug 26]. Available from: https://ico.org.uk/for-organisations/uk-gdpr-guidance-and-resources/data-sharing/anonymisation/introduction-to-anonymisation/
13. ADS-Limathon Limited. i-BLIPS [internet]. ADS-Limathon Limited; [cited 2025 Aug 26]. Available from: https://www.i-blips.com/
14. Brunner HI, Feldman BM, Urowitz MB, Gladman DD. Item weightings for the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index using Rasch analysis do not lead to an important improvement. J Rheumatol. 2003;30(2):292-7.
15. StataCorp LLC. Stata Statistical Software: Release 18.1 [computer program]. College Station (TX): StataCorp LLC; 2024.