‘Not at target’: prevalence and consequences of inadequate disease control in systemic lupus erythematosus—a multinational observational cohort study

Rangi Kandane-Rathnayake1, Worawit Louthrenoo2, Alberta Ho1, Shue-Fen Luo3, Yeong-Jian J. Wu3, Yi-Hsing Chen4, Jiacai Cho5, Aisha Lateef6, Laniyati Hamijoyo6, Sandra V. Navarra7, Leonid Zamora7, Sargunan Sockalingam8, Yuan An9, Zhanguo Li9, Masayoshi Harigai10, Yajie Hao11, Zhuoli Zhang11, Jun Kikuchi12, Tsutomu Takeuchi12, B. M. D. B. Basnayake13, Madelynn Chan14, Kristine Pek Ling Ng15, Nicola Tugnet16, Sunil Kumar17, Shereen Oon18, Fiona Goldblatt19, Sean O’Neill20, Kathryn A. Gibson20,21, Naoaki Ohkubo22, Yoshiya Tanaka22, Sang-Cheol Bae23, Chak Sing Lau24, Mandana Nikpour18, Vera Golder1, Eric F. Morand1* and For the Asia-Pacific Lupus Collaboration

Abstract

Background: The unmet need in systemic lupus erythematosus (SLE) with the current standard of care is widely recognised, but few studies have quantified this. The recent definition of treat-to-target endpoints and other thresholds of uncontrolled disease activity provide an opportunity to formally define unmet need in SLE. In this study, we enumerated the prevalence of these states and examined their association with adverse outcomes.

Methods: Data were collected prospectively in a 13-country longitudinal SLE cohort between 2013 and 2019. Unmet need was defined as never attaining lupus low disease activity state (LLDAS), a time-adjusted mean SLEDAI-2K (AMS) > 4, or ever experiencing high disease activity status (HDAS; SLEDAI-2K ≥10). Health-related quality of life (HRQoL) was assessed using SF36 (v2) and damage accrual using the SLICC-ACR SLE Damage Index (SDI).

Results: A total of 3384 SLE patients were followed over 30,313 visits (median [IQR] follow-up 2.4 [0.4, 4.3] years). Eight hundred thirteen patients (24%) never achieved LLDAS. Median AMS was 3.0 [1.4, 4.9]; 34% of patients had AMS > 4. Twenty-five per cent of patients had episodes of HDAS. Each of LLDAS-never, AMS > 4, and HDAS-ever was strongly associated with damage accrual, higher glucocorticoid use, and worse HRQoL. Mortality was significantly increased in LLDAS-never (adjusted HR [95% CI] = 4.98 [2.07, 12.0], p<0.001) and HDAS-ever (adjusted hazard ratio [HR] [95% CI] = 5.45 [2.75, 10.8], p<0.001) patients.

*Correspondence: eric.morand@monash.edu
1 Monash Medical Centre, School of Clinical Sciences, Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia
Full list of author information is available at the end of the article

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
**Conclusion:** Failure to achieve LLDAS, high average disease activity, and episodes of HDAS were prevalent in SLE and were significantly associated with poor outcomes including organ damage, glucocorticoid exposure, poor quality of life, and mortality.

**Keywords:** Systemic lupus erythematosus, Disease activity, Outcomes, Quality of life, Unmet need

**Background**
Systemic lupus erythematosus (SLE, or lupus) is characterised by recurrent immune-mediated inflammatory damage in multiple organ systems [1], resulting in a marked loss of life expectancy [2] and among the top 10 causes of death in young women in the USA [3]. SLE treatment has changed little in the past 50 years due to the paucity of approved or reimbursed novel therapies [4]. As a result, the majority of patients are still treated with non-specific agents including glucocorticoids, which can contribute to harmful long-term outcomes that include irreversible organ damage [5]. The failure to improve SLE outcomes is in stark contrast to paradigm changes in outcomes in other autoimmune diseases such as rheumatoid arthritis (RA). Transformation of patient outcomes in RA began with the recognition that historical standards of care were associated with poor outcomes, followed by treat-to-target strategies driven by validated thresholds of inadequate response. While patient outcomes in RA, including mortality, have been transformed in the last 20 years in response to these approaches [6], there has been no such improvement in SLE in the same period [7].

To date, only two targeted therapy has received regulatory approval for SLE treatment. Belimumab, a monoclonal antibody (mAb) targeted against the B cell activating factor (BAFF) [8], was approved in the USA in 2011 for active SLE [9] and lupus nephritis [10], but uptake has been low in many care settings including in the USA [11]. Very recently, anifrolumab, a type 1 interferon receptor antagonist, received FDA approval for the treatment of SLE [12, 13]. As more advanced therapies for SLE emerge, the proportion of SLE patients whose disease characteristics identify them as having unmet need that might justify such therapies is unknown. Identifying the proportion of SLE patients who could benefit from advanced therapies could assist physicians, hospitals, and regulators to plan for their use, help patient groups lobby for reimbursement of SLE drugs, and plug gaps in understanding in the wider medical community about the needed changes in SLE treatment.

A limiting factor on quantifying unmet need in SLE has been a lack of formal definitions. The recent prospective validation of the Lupus Low Disease Activity State (LLDAS) [14] as affording time-dependent protection from adverse outcomes, findings confirmed for both damage accrual and mortality in independent studies [15, 16], indicates that failure to attain LLDAS is an undesirable disease state. Other measures of inadequate disease control have also recently emerged, which allow the enumeration of proportions of patients with indicators consistent with inadequate disease control, and who therefore have the potential to benefit from treatment advances.

**Methods**

**Aim**
In this study, we aimed to evaluate the prevalence, and consequences, of potential unmet need in SLE, using recently defined descriptors of inadequate disease control.

**Study population**
Data from the Asia Pacific Lupus Collaboration (APLC) patient cohort, collected prospectively between 2013 and 2019, were used to conduct this study. Patients were recruited from 23 sites across 13 countries. All patients met either the 1997 American College of Rheumatology (ACR) Modified Classification Criteria for SLE [17] or the Systemic Lupus International Collaborating Clinics (SLICC) 2012 Classification Criteria [18] and provided written informed consent [19].

**Data collection**
Data were collected during routine patient follow-up visits using standardised electronic or paper data-collection forms. The minimum prescribed visit frequency was 6 months, with the majority of patients having more frequent visits based on clinical need.

Baseline demographic data were collected at enrolment and included age, gender, self-reported ethnicity, date of onset of SLE, date of SLE diagnosis, smoking status, highest education level, and family history. At each visit, SLE Disease Activity Index (SLEDAI)-2K [20], SELENA-SLEDAI flare index [21], and physician global assessment (PGA 0–3) [22], and data on all medications and doses, were collected. Organ damage was measured at baseline and annually using the SLICC-ACR Damage Index (SDI) [23]; a change of one unit in SDI has been demonstrated to be clinically significant [24] and was chosen to define damage accrual. Health-related quality of life (HRQoL)
was captured using the Short Form 36 (v2) (SF36) and expressed as mental and physical component summary (MCS and PCS, respectively) scores, as described [25].

**Definitions of unmet need**

LLDAS was defined on a per-visit basis according to the recently validated definition of Golder et al. [14]. Briefly, this includes the requirement for all of SLEDAI-2K ≤ 4, excluding major organ activity, absence of new SLEDAI-2K activity compared to the preceding visit, PGA ≤ 1 (0–3), and daily prednisolone dose ≤ 7.5 mg/day; anti-malarials and immunosuppressant use are permitted. A time-adjusted mean SLEDAI-2K (AMS) was calculated as a measure of disease activity over time [26], and time-adjusted mean PGA and prednisolone dose similarly calculated. High disease activity status (HDAS; SLEDAI-2K ≥ 10) was documented as described [27, 28]. Inadequate disease control was classified as follows: patients never achieving LLDAS during the period of observation (LLDAS-never); persistent active disease defined as AMS > 4, meaning that on average the SLEDAI-2K was always above 4 throughout the period of observation; or exhibiting HDAS at any time (HDAS-ever) [27, 28].

**Statistical analysis**

Statistical analyses were performed using Stata V. 15.1 (StataCorp, College Station, TX, USA). Continuous variables were described as median and interquartile range (IQR) due to the skewed nature of the data and compared using Wilcoxon rank-sum tests. Categorical variables were described as frequency (%) and compared using $\chi^2$ tests. In all analyses, a $p$-value ≤ 0.05 was considered statistically significant.

Survival (time-to-event) analyses, i.e. Cox regression models, were used to examine the associations of unmet need definitions with damage accrual and mortality. When performing survival analyses with damage accrual, we incorporated Prentice, Williams and Peterson modelling with gap time (PWP-GT) to set up the data to allow multiple ‘failures’ per patient as some patients accrued damage more than once during the study observation period. In addition, clustering was specified in these Cox regression models to account for intragroup correlation. The results from the time-dependent Cox regression analyses are presented as hazard ratios with corresponding 95% confidence intervals (CI).

Furthermore, generalised estimating equations (GEE) methods were used to examine the associations of unmet need definitions with prednisolone dose and HRQoL assessed using SF36. These outcomes were captured as continuous variables; therefore, GEE models were specified for Gaussian distribution, identity link, and exchangeable correlation matrix. Regression coefficients estimated from GEE analyses represented the change in estimated population averages, i.e. mean changes, which we reported with corresponding 95% CI.

**Results**

We studied 3384 SLE patients who were followed over median [IQR] 2.4 [0.4, 4.3] years, comprising 30,313 visits. The median [IQR] age at enrolment was 39 [30, 50], 3109 (92%) of patients were female, and the majority were of Asian ethnicity (Table 1).

We first assessed unmet need defined by non-attainment of LLDAS. LLDAS status was not determined for 2.6% of visits, due predominantly to missing PGA or incomplete SLEDAI-2K. Overall, patients were in LLDAS in 13,447/28,760 visits (47%), and consequently, not in LLDAS in 15,223 visits (53%), and the median percentage of observed time each patient spent in LLDAS was 45.8% [IQR 8.5, 73.8] (range: 0, 100) (Table 1). Eight hundred thirteen patients (24.3%) never achieved LLDAS during the observation period (LLDAS-never). Two hundred forty-one patients (7%) met all three definitions (Fig. 1).

Characteristics of patients stratified by LLDAS attainment are shown in Table 2. Compared to patients who ever attained LLDAS, patients who never achieved LLDAS were younger, more likely to be of Asian ancestry, and had shorter median follow-up (Table 2). Compared to patients who ever achieved LLDAS, LLDAS-never was associated with significantly higher disease activity over time measured by SLEDAI-2K or PGA, higher glucocorticoid dosing, and increased mortality, as well as significantly lower HRQoL measured by both MCS and PCS (Table 2).

We next assessed a definition of persistent active disease over time, defined as AMS > 4, meaning on average a patient’s SLEDAI-2K was above 4 throughout the period of observation. The median AMS in the cohort was 3.0 [IQR 1.4, 4.9] (range: 0, 22) and 932 patients (34%) had AMS > 4 (Table 1). Compared to patients with AMS ≤ 4, patients with AMS > 4 were younger and more likely to be Asian and were more likely to have serological activity (Table 2). In terms of outcomes, AMS > 4 was associated with significantly higher glucocorticoid dosing, more flares, more damage accrual, and higher mortality, as well as significantly less time in LLDAS and lower HRQoL measured by both MCS and PCS (Table 2).

HDAS (SLEDAI-2K ≥ 10) has recently been defined as a state associated with worse outcomes in SLE even if only experienced once [27, 28]. Eight hundred fifty-one patients (25%) had HDAS at least once during the study period, accounting for 8% ($n$=2418) of all visits. Compared to patients who never experienced HDAS
during the period of observation, HDAS-ever patients were younger and had a more recent onset of disease and increased serological activity, but HDAS was not associated with ethnicity (Table 2). In terms of disease outcomes, HDAS-ever was associated with higher disease activity across the observation period measured by SLEDAI-2K or PGA, higher glucocorticoid doses, more flares, less time in LLDAS, and higher rates of both damage accrual and death (Table 2). In addition, HRQoL (MCS and PCS) was lower in HDAS-ever patients (Table 2).

Each of LLDAS-never, AMS>4, and HDAS-ever was strongly associated with poor outcomes over time, including more damage accrual, higher risk of mortality, high glucocorticoid use, and worse SF36 PCS and MCS scores reflecting poor HRQoL (Table 3 and
Supplementary tables S1, S2, S3, S4, S5). For example, never attaining LLDAS was associated with a near-5-fold risk of death after adjustment for confounders (Table 3 and Supplementary Table S1). In the HDAS group, the instantaneous risk (hazard) of mortality was more than five times that of patients without HDAS after adjustment for confounders (adjusted HR 5.45 (2.75,10.80), \( p < 0.001 \) (Table 3 and Supplementary Table S2).

The use of standard of care medications in the unmet need patient population was also evaluated. As SLE treatments change over time in individual patients, these data were analysed on a per-visit basis. Unmet need status did not appear to be due to under-treatment. For example, over 70% of LLDAS–never patients were receiving combination therapy with at least two of anti-malarials, glucocorticoids, and immunosuppressants, and fewer than 10% were on no treatment or anti-malarial monotherapy (Table 4). Similar profiles of medication use were observed for the other definitions (Table 4).

**Discussion**

The standard of care for SLE has changed little in recent decades, with only two new therapy approved for active SLE in the last 50 years. Accompanying this paucity of treatment innovation, improvements in SLE mortality observed in the late twentieth century have plateaued in the first decades of the twenty-first century [7]. This is in contrast to outcomes in RA, which have dramatically improved in the same period [6]. The ability to harness new therapies in treat-to-target approaches to SLE management, as recently advocated [4, 29, 30], requires additions to the current knowledge base. Ultimately, formal treat-to-target studies should be performed, using failure to attain well-validated endpoints to trigger treatment escalation, and using long-term harm as the outcome measure. Before this, however, access to such treatments is required, and understanding the extent of unmet need is needed in order to inform physicians and regulators. Here, we have used recently defined and/or validated indices of inadequate disease control, and a large multinational longitudinal SLE cohort, to evaluate the extent and consequences of unmet need in SLE patients receiving standard of care.

Our findings demonstrate that unmet need in SLE is prevalent and is associated with poor outcomes. In this large dataset, half of patients’ observed time overall was spent not in LLDAS, and a quarter of patients did not attain LLDAS at any time across the period of...
observation. In turn, non-attainment of LLDAS was associated with higher overall disease activity and glucocorticoid exposure, as well as more damage accrual and lower HRQoL. Strikingly, never attaining LLDAS was associated with a near fivefold increase in mortality. LLDAS attainment has been shown in multiple retrospective cohort studies, and recently in a prospective multicentre study, to be associated with protection from SLE flare, damage accrual, and death, and to be associated with improved HRQoL [14–16, 25], and where studied these associations are dose-dependent, i.e. less time in LLDAS is associated with poorer outcomes [14, 31]. While the associations of never attaining LLDAS with worse outcomes were therefore expected, the observation that a quarter of patients did not attain LLDAS on even a single occasion signifies that this treat to target goal is insufficiently frequently met with the current standard of care.

Other definitions of potential unmet need showed similar findings. A SLEDAI-2K of greater than four is regarded as indicating active disease. We used AMS > 4 as a measure of poor control of disease activity; patients with AMS > 4 had an average SLEDAI-2K > 4 over the entire period of observation. One-third of patients had AMS > 4, consistent with enduringly poorly controlled...
Table 3  Longitudinal associations of outcomes with different SLE unmet need definitions

| Outcomes          | LLDAS-never | AMS > 4 | HDAS-ever |
|-------------------|-------------|---------|-----------|
| **Damage accrual**|             |         |           |
| Unadjusted        | HR1 (95% CI), p-value | HR1 (95% CI), p-value | HR1 (95% CI), p-value |
|                   | 1.52 (1.31, 1.76), p < 0.001 | 1.38 (1.18, 1.61), p < 0.001 | 1.85 (1.47, 2.31), p < 0.001 |
| Adjusted          | 1.46 (1.26, 1.69), p < 0.001 | 1.36 (1.16, 1.59), p < 0.001 | 1.81 (1.43, 2.30), p < 0.001 |
| **Mortality**     |             |         |           |
| Unadjusted        | 6.64 (2.83, 15.6), p < 0.001 | 2.99 (1.68, 5.3), p < 0.001 | 6.97 (3.82, 12.7), p < 0.001 |
| Adjusted          | 4.98 (2.07, 12.0), p < 0.001 | 2.36 (1.29, 4.33), p = 0.006 | 5.45 (2.75, 10.80), p < 0.001 |

| Cumulative prednisolone (PNL) |       |       |           |
| Unadjusted          | 5.61 (5.34, 5.88), p < 0.001 | 4.08 (3.66, 4.51), p < 0.001 | 8.96 (8.02, 9.91), p < 0.001 |
| Adjusted            | 5.71 (5.38, 6.03), p < 0.001 | 3.39 (2.95, 3.83), p < 0.001 | 9.04 (7.80, 10.3), p < 0.001 |
| TAM-PNL at visit    |       |       |           |
| Unadjusted          | 1.25 (1.08, 1.41), p < 0.001 | 2.33 (1.90, 2.76), p < 0.001 | 1.18 (0.88, 1.47), p < 0.001 |
| Adjusted            | 1.35 (1.17, 1.52), p < 0.001 | 2.52 (2.20, 2.85), p < 0.001 | 1.41 (0.88, 1.94), p < 0.001 |
| **PCS**            |       |       |           |
| Unadjusted          | −1.59 (−1.90, −1.28), p < 0.001 | −1.04 (−1.58, −0.50), p < 0.001 | −2.49 (−3.07, −1.90), p < 0.001 |
| Adjusted            | −1.40 (−1.71, −1.09), p < 0.001 | −0.96 (−1.50, −0.43), p < 0.001 | −2.17 (−2.78, −1.57), p < 0.001 |
| **MCS**            |       |       |           |
| Unadjusted          | −1.22 (−1.58, −0.85), p < 0.001 | −0.84 (−1.42, −0.27), p < 0.001 | −1.37 (−2.03, −0.70), p < 0.001 |
| Adjusted            | −1.20 (−1.57, −0.84), p < 0.001 | −0.97 (−1.56, −0.38), p = 0.001 | −1.29 (−1.96, −0.63), p < 0.001 |

1 Hazard ratios (HR) derived using Cox regression analyses. 2 Regression coefficients (RCs) derived using generalised estimating equations (GEE). RC indicates the mean difference between the unmet need definition and the corresponding comparator (e.g. not in LLDAS vs. in LLDAS). TAM-PNL at visit = time-adjusted mean prednisolone since the baseline visit to each routine visit.

a HRs adjusted for age, disease duration, Asian ethnicity, tertiary education, and cumulative PNL. Full multivariable models are presented in Supplementary table S1.
b HRs adjusted for cumulative PNL and ACR/SLICC SDI score. Full multivariable models are presented in Supplementary table S2.
c RCs adjusted for age, disease duration, Asian ethnicity, presence of flare, and ACR/SLIC SDI score. Full multivariable models for prednisolone are presented in Supplementary table S3.
d RCs adjusted for age, disease duration, Asian ethnicity, tertiary education, cumulative PNL, presence of flare, and organ damage. Full multivariable models are presented in Supplementary table S4.
e RCs adjusted for Asian ethnicity, tertiary education, and cumulative PNL. Full multivariable models are presented in Supplementary table S5.

Table 4  Medication use, stratified by patient visits meeting unmet need definitions

| Medications (therapy) | All visits Total = 30,313 n (%) | LLDAS-never Total = 15,223 n (%) | AMS > 4 Total = 7925 n (%) | HDAS-ever Total = 2418 n (%) |
|-----------------------|---------------------------------|----------------------------------|----------------------------|-----------------------------|
| No therapy            | 1553 (5.12)                     | 383 (2.52)                       | 189 (2.38)                 | 39 (1.61)                   |
| Monotherapy           | 9167 (30.2)                     | 4015 (26.4)                      | 2014 (25.4)                | 515 (21.3)                  |
| PNL alone             | 5222 (17.2)                     | 2816 (18.5)                      | 1391 (17.6)                | 412 (17.0)                  |
| AM alone              | 3567 (11.8)                     | 1034 (6.79)                      | 543 (6.85)                 | 81 (3.35)                   |
| IS alone              | 378 (1.25)                      | 165 (1.08)                       | 80 (1.01)                  | 22 (0.91)                   |
| Dual therapy          | 12,935 (42.7)                   | 6957 (45.7)                      | 3604 (45.5)                | 1237 (51.2)                 |
| PNL + AM              | 7902 (26.1)                     | 4270 (28.1)                      | 2281 (28.8)                | 841 (34.8)                  |
| PNL + IS              | 3610 (11.9)                     | 2224 (14.6)                      | 1079 (13.6)                | 369 (15.3)                  |
| AM + IS               | 1423 (4.7)                      | 463 (3.04)                       | 244 (3.08)                 | 27 (1.12)                   |
| Triplet therapy (PNL+AM+IS) | 6658 (22) | 3868 (25.4) | 2118 (26.7) | 627 (25.9) |
| Combination therapy (dual/triple) | 19,593 (64.6) | 10,825 (71.1) | 5722 (72.2) | 1864 (77.1) |
disease activity across the period of observation, and this state was associated with increased flares, glucocorticoid use, mortality, and damage accrual, as well as lower HRQoL. Another simple index of poor disease control, HDAS, recently was demonstrated to be associated with poor outcomes in SLE observational cohorts even if only exhibited once during a period of observation [27, 28]. HDAS was observed at least once in a quarter of all patients, and the association of this state on even a single occasion spanned the same adverse outcomes as AMS>4, including a strong association with mortality. This suggests that even single episodes of HDAS are associated with an adverse impact on patient outcomes, a finding similar to that recently reported in a single-centre cohort study [28], and that these single episodes are comparable in outcome to persistently active disease at a lower threshold. Interestingly, all the definitions of unmet need tested here were also associated with younger age of disease onset; this may have parallels in the observation that earlier disease onset in SLE is linked with higher genetic risk scores and worse outcomes [32].

These data using empirical cut-offs demonstrate formally that many SLE patients remain inadequately controlled in the setting of current standards of care. This raises the question of whether treatments could improve outcomes for patients so identified. Of note, we have recently described an algorithm for identifying HDAS episodes from SLE patient medical records without the need for SLEDAI-2K scores [27]. Such patients may be more likely to respond to targeted interventions. Increased responses to therapy with atacicept were seen in SLE patients with HDAS at baseline [33], and the same SLEDAI cut-off (≥10) which defines HDAS was associated with increased likelihood of response to treatment with belimumab in post hoc analysis [34]. This same analysis by Van Vollenhoven et al. also showed associations of response to belimumab with serological activity, i.e. low complement and/or anti-dsDNA, and glucocorticoid treatment [34]. We analysed the combination of these factors, i.e. HDAS, serological activity, and glucocorticoid treatment, and found that 23.1% of patients met these criteria at least once, and doing so was associated with similar if not greater associations with poor outcomes such as damage accrual, low quality of life, and mortality (data not shown). Although it is possible that these findings relate less to responsiveness per se than to the ability to measure a response using existing trial endpoints [35], identifying patients who exhibit metrics consistent with unmet need may enable targeting for treatment escalation or enrolment in clinical trials.

There are several limitations to the interpretation of this study. First, the research question was designed and data analysed retrospectively, although data were collected prospectively using standardised data collection forms. Secondly, no inference about the potential response to an intervention in patients who meet these unmet need criteria can be drawn in the absence of a study of such an intervention. Thirdly, this multicentre study was performed in the Asia-Pacific region in a cohort of majority with Asian ancestry and variations in health systems including access to biologicals that may impact our results, although the patterns of medication use were broadly similar to those reported in other cohorts.

**Conclusion**

In conclusion, this study of a large multicentre cohort indicates a high prevalence of unmet need in SLE, defined using empirical thresholds, and that the consequences of these states of unmet need include increased damage, increased mortality, and reduced quality of life. Unmet need in SLE is a prevalent and serious issue, and improved therapeutic strategies are urgently needed.

**Abbreviations**

ACR: American College of Rheumatology; AMS: Adjusted mean SLEDAI; APLC: Asia Pacific Lupus Collaboration; BAFF: B cell activating factor; CI: Confidence intervals; GEE: Generalised estimating equations; HRQoL: Health-related quality of life; HDAS: High disease activity status; HR: Hazard ratio; IQR: Interquartile range; LLDAS: Lupus Low Disease Activity State; MCS: Mental component summary; MUHREC: Monash University Human Research Ethics Committee; PCS: Physical component summary; PGA: Physician Global Assessment; PWP-Prentice, Williams and Peterson modelling with gap time; RA: Rheumatoid arthritis; SDI: SLICC-ACR Damage Index; SLE: Systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; TAM: Time-adjusted mean.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13075-022-02756-3.

**Additional file 1**: Supplementary Table S1. Associations of SLE unmet need definitions with organ damage accrual, adjusted for other potential confounding factors.

**Additional file 2**: Supplementary Table S2. Associations of SLE unmet need definitions with mortality, adjusted for other potential confounding factors.

**Additional file 3**: Supplementary Table S3. Associations of SLE unmet need definitions with daily prednisolone dose (mg), adjusted for other potential confounding factors.

**Additional file 4**: Supplementary Table S4. Associations of SLE unmet need definitions with SF36-PCS, adjusted for other potential confounding factors.

**Additional file 5**: Supplementary Table S5. Associations of SLE unmet need definitions with SF36-MCS, adjusted for other potential confounding factors.

**Acknowledgements**

We thank all the participants in the Asia Pacific Lupus Collaboration (APLC) for their participation and all the data collectors across the region for their ongoing support for the APLC research activities.
Authors’ contributions
RK-R was involved in the study design, conducted the statistical analysis, interpreted results, and was a major contributor in writing the manuscript. EM was involved in the study design, interpreted results, and was a major contributor in writing the manuscript. WL, AH, SF, Y-JW, Y-HC, JC, AL, LH, SN, LZ, SS, YA, ZL, YK, MH, YH, ZZ, JK, TT, BB, MC, KN, NT, SK, SO, FG, SON, KG, NO, YT, S-CB, CSL, MN, and VG all contributed to data acquisition, interpretation of results, and manuscript review. All authors read and approved the final manuscript.

Funding
The APLC has received unrestricted project grants from AstraZeneca, BMS, Eli Lilly, Janssen, Merck Serono, and UCB in support of data collection contributing to this work. The APLC received funding from GlaxoSmithKline Australia to conduct this research study.

Availability of data and materials
The data underlying this article cannot be publically shared due to the strict protocols and procedures outlined in the Asia Pacific Lupus Collaboration (APLC) Data Access Policy to protect patients’ privacy and to maintain data security and ethical principles.

Declarations

Ethics approval and consent to participate
Each APLC participating site has obtained local ethics approval to participate in research activities, as described (15). Monash University Human Research Ethics Committee (MUHREC) has provided approval to store the central dataset and to perform analyses using the pooled data and for publication of results. This study is approved by the MUHREC Project ID 18778.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Author details
1 Monash Medical Centre, School of Clinical Sciences, Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia. 2 Chang Mai University, Chang Mai, Thailand. 3 Chang Gung Memorial Hospital, Taoyuan County and Keelung, Taiwan. 4 Taichung Veterans General Hospital, Taichung, Taiwan. 5 National University Hospital, Singapore, Singapore. 6 University of Padjadjaran, Bandung, Indonesia. 7 University of Santo Tomas Hospital, Manila, Philippines. 8 University of Malaya, Kuala Lumpur, Malaysia. 9 People’s Hospital Peking University Health Science Centre, Beijing, China. 10 Tokyo Women’s Medical University, Tokyo, Japan. 11 Peking University First Hospital, Beijing, China. 12 Keio University, Tokyo, Japan. 13 Teaching Hospital, Kandy, Sri Lanka. 14 Tan Tock Seng Hospital, Singapore, Singapore. 15 Waiwai District Health Board, Auckland, New Zealand. 16 Auckland District Health Board, Auckland, New Zealand. 17 Midwellmore Hospital, Auckland, New Zealand. 18 The University of Melbourne at St Vincent’s Hospital, Fitzroy, Victoria, Australia. 19 Royal Adelaide Hospital and Flinders Medical Centre, Adelaide, Australia. 20 University of New South Wales and Ingham Institute of Applied Medical Research, Liverpool, Australia. 21 Eli Lilly Pty Ltd. Australia, Liverpool Hospital, Sydney, Australia. 22 University of Occupational and Environmental Health, Kiyotakuychu, Japan. 23 Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea. 24 University of Hong Kong, Pok Fu Lam, Hong Kong.

Received: 1 August 2021 Accepted: 28 February 2022 Published online: 14 March 2022

References
1. Bruce IN, O’Keeffe AG, Farewell VJ, Hanly JG, Manzi S, Su L, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (SLICC) inception cohort. Ann Rheum Dis. 2015;74(9):1706–13.
2. Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol. 2008;35(11):2152–8.
3. Yen EY, Singh RR. Brief report: lupus–an unrecognized leading cause of death in young females: a population-based study using nationwide death certificates, 2000–2015. Arthritis Rheum. 2018;70(8):1251–5.
4. Franklyn K, Hoi A, Nikpour M, Morand EF. The need to define treatment goals for systemic lupus erythematosus. Nat Rev Rheumatol. 2014;10(9):567–71.
5. Apostolopoulos D, Kandane-Rathnayake R, Loutheenoo W, Luo SF, Wu YJ, Lateef A, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus with no clinical or serological disease activity: a multicentre cohort study. Lancet Rheumatol. 2020;2(1):e24–30.
6. Zhang Y, Lu N, Peloquin C, Dubreuil M, Neogi T, Aviña-Zubieta JA, et al. Improved survival in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis. 2017;76(2):408–13.
7. Jorge AM, Lu N, Zhang Y, Rai SK, Choi HK. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999–2014). Rheumatology (Oxford). 2018;57(2):337–44.
8. Vincent FB, Morand EF, Schneider P, Mackay F. The BAFF/APRIL system in SLE pathogenesis. Nat Rev Rheumatol. 2014;10(6):365–73.
9. Funre R, Petri M, Zamanii O, Cervera R, Wallace DJ, Tegzova D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918–3930.
10. Funre R, Kovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020;383(2):1117–1218.
11. Bell CF, Priest J, Stott-Miller M, Kan H, Amelio J, Song X, et al. Real-world treatment patterns, healthcare resource utilisation and costs in patients with systemic lupus erythematosus treated with belimumab: a retrospective analysis of claims data in the USA. Lupus Sci Med. 2020;7(1):e000357.
12. Burki TK. FDA approval for anifrolumab in patients with lupus. The Lancet Rheumatology. 2021;3(10):E689.
13. Morand EF, Funre R, Tanaka Y, Bruce IN, Richne C, Bae S-C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(5):211–21.
14. Golder V, Kandane-Rathnayake R, Huq M, Nim H, Loutheenoo W, Luo SF, et al. Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. Lancet Rheumatol. 2019;1(2):E95-E102.
15. Sharma C, Raymond W, Elertsen G, Nossent J. Achieving lupus low disease activity state (LLDAS)‑50 is associated with both reduced damage accrual and mortality in patients with systemic lupus erythematosus. Arthritis Care Res. 2019;72(3):447–451.
16. Piga M, Floris A, Cappellazzo G, Chessa E, Congia M, Mathieu A, et al. Failure to achieve lupus low disease activity state (LLDAS) 6 months after diagnosis is associated with early damage accrual in Caucasian patients with systemic lupus erythematosus. Arthritis Res Ther. 2017;19(1):247.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
18. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677–86.
19. Kandane-Rathnayake R, Golder V, Loutheenoo W, Luo SF, Jan Wu YJ, Li Z, et al. Development of the Asia Pacific Lupus Collaboration cohort. Int J Rheum Dis. 2019;22(3):425–33.
20. Toma Z, Urowitz MB, Ibanez D, Gladman DD. SLEDAI-2K 10 days versus SLEDAI-2K 30 days in a longitudinal evaluation. Lupus. 2011;20(1):67–70.
21. Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcon GS, Aranow C, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis. 2011;70(1):54–9.
22. Chessa E, Piga M, Floris A, Devilliers H, Cauli A, Arnaud L. Use of Physician Global Assessment in systemic lupus erythematosus: a systematic review of its psychometric properties. Rheumatology. 2020;59(12):3622–3632.
23. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the systemic lupus international
24. Chambers SA, Allen E, Rahman A, Isenberg D. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. Rheumatology. 2009;48(6):673–5.

25. Golder V, Kandane-Rathnayake R, Hoi AV, Huq M, Louthrenoo W, An Y, et al. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. Arthritis Res Ther. 2017;19(1):62.

26. Ibañez D, Gladman D, Urowitz M. Summarizing disease features over time: I. adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol. 2003;30(9):1977–82.

27. Hoi A, Nim HT, Koelmeyer R, Sun Y, Kao A, Gunther O, et al. Algorithm for calculating high disease activity in SLE. Rheumatology (Oxford). 2021;60(9):4291–4297.

28. Koelmeyer R, Nim HT, Nikpour M, Sun YB, Kao A, Guenther O, et al. High disease activity status suggests more severe disease and damage accrual in systemic lupus erythematosus. Lupus Sci Med. 2020;7:e000372. https://doi.org/10.1136/lupus-2019-000372.

29. van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lenstrom K, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis. 2014;73(8):958–67.

30. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. Update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019;78(6):annrheumdis-2019-215089-745.

31. 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(11):1790–1795.

32. Reid S, Alesson A, Frodlund M, Morris D, Sandling JK, Bolin K, et al. High genetic risk score is associated with early disease onset, damage accrual and decreased survival in systemic lupus erythematosus. Ann Rheum Dis. 2020;79(3):363–9.

33. Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA, Chang P, et al. Efficacy and safety of atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. Arthr Rheumatol (Hoboken, NJ). 2018;70(2):266–76.

34. van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis. 2012;71(8):1343–9.

35. Connelly K, Golder V, Kandane-Rathnayake R, Morand EF. Clinician-reported outcome measures in lupus trials: a problem worth solving. Lancet Rheumatol. 2021;3(8):E595–E603.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.