Published in final edited form as:

Lupus. 2019 December ; 28(14): 1648–1655. doi:10.1177/0961203319886028.

Predictors of Predominant Lupus Low Disease Activity State (LLDAS-50).

Hakan Babaoglu, M.D.^{1,2} [Lupus Fellow, Rheumatology Fellow.], Jessica Li, M.P.H.¹ [Biostatistician.], Daniel Goldman, Ph.D., M.Sc.¹ [Assistant Professor of Medicine.], Laurence S Magder, M.P.H., Ph.D.³ [Professor of Medicine.], Michelle Petri, M.D., M.P.H.¹ [Professor of Medicine.]

¹Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

²Division of Rheumatology, Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey.

³Department of Epidemiology and Public Health, University of Maryland, Baltimore, Maryland, USA

Abstract

Aim: The Lupus Low Disease Activity State (LLDAS) is a potential treat to target goal in systemic lupus erythematosus (SLE). SLE patients, in LLDAS for more than half of the observation time, have about a 50% lower risk of new organ damage and have reduced mortality. We identified predictors of being in LLDAS 50% of the observation time.

Methods: A total of 2228 SLE patients, who had at least three clinical visits, were included. Percentage of time in LLDAS was calculated based on the proportion of days under observations. LLDAS-50 was defined as being in LLDAS for 50% of the observation time. We used the stepwise selection procedure in logistic regression to identify predictors of LLDAS-50.

Results: 1169 (52.5%) of SLE patients, but only 37.6% of African-Americans, achieved LLDAS-50. In the multivariable model, African-American ethnicity, hypocomplementemia, serositis, renal activity, arthritis, anti-RNP, anti-dsDNA, vasculitis, malar rash, discoid rash, thrombocytopenia, and immunosuppressive use were negative predictors of LLDAS-50. Older age at diagnosis, longer disease duration, higher education level, and greater percentage of time taking hydroxychloroquine remained positive predictors of LLDAS-50

Conclusion: In this large cohort, only 52.5% achieved LLDAS-50. This proportion was even less in African-Americans. A higher percentage of time taking hydroxychloroquine was a modifiable positive predictor of LLDAS-50. Anti-RNP, anti-dsDNA and low complement were negatively associated with LLDAS-50. Our findings further emphasize the importance of inclusion of African-Americans in clinical trials and hydroxychloroquine adherence in both clinical practice and clinical trials.

Corresponding Author: Michelle Petri, M.D., M.P.H., mpetri@jhmi.edu, Division of Rheumatology, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205. Phone: 410-955-3823, Fax: 410-614-0498.

Conflicts of Interests The authors have no related COIs to disclose.

Introduction

The clinical course of systemic lupus erythematosus (SLE) is highly variable among individuals and over time¹. Both chronic disease activity and flares are associated with long-term organ damage and mortality². Despite recent improvements in the management of SLE, patients with SLE still have a high risk of morbidity and mortality³. Achieving sustained remission is the ultimate goal of management of SLE, but it is rare⁴. Recently, a new potential treat to target goal, the Lupus Low Disease Activity State, was developed and validated by the Asia-Pacific Lupus Collaboration⁵. LLDAS combines both low SLE activity and a low prednisone dose (less than or equal to 7.5 mg daily). An increasing number of studies have applied LLDAS and found that LLDAS is an achievable target state and associated with a lower risk of new damage accrual⁵⁻⁹ and better health-related quality of life¹⁰. LLDAS has been found as a discriminatory endpoint in post-hoc analyses of successful clinical trials^{11, 12} and in a prospective clinical trial¹³.

Although there is no minimal duration requirement to fulfill the definition of LLDAS, as one might expect, greater percentage of time in LLDAS⁷⁻⁹ and longer consequent duration of LLDAS⁶ result in a better protective effect against organ damage. Furthermore, over 50 percent of time in LLDAS was associated with reduced mortality¹⁴.

A few studies have analyzed the predictors of duration of time in LLDAS. Tani et al. reported that 36.5% of their 115 Italian SLE patients achieved LLDAS for at least 5 years. Higher SLEDAI at baseline, joint and skin involvement were found as negative predictors of 5 consecutive years in LLDAS⁹. Zen et al. found that 75.4% of their 293 Caucasian SLE patients were in LLDAS for at least two consecutive years. Baseline higher SLEDAI-2K, Physician Global Assessment (PGA) score more than 1, joint and skin involvement, methotrexate or cyclosporin treatment, higher prednisone dose and serositis, vasculitis, and treatment with immunosuppressive drugs during the disease course were found as negative predictors of two consecutive years in LLDAS⁶.

Although over 50 percent of time in LLDAS ("LLDAS-50") is associated with both reduced damage and mortality^{5, 14}, studies of predictors of LLDAS-50 are lacking. Defining predictors of LLDAS-50 would be useful for stratification in clinical trials and for disease management. In this study, we addressed predictors of being in LLDAS 50% of the observation time in a large SLE cohort with both Caucasian and African-American representation.

Methods

The Hopkins Lupus Cohort is a prospective longitudinal single-center cohort of SLE patients ongoing since 1987. It was approved on an annual basis by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent to participate. Visits were scheduled quarterly by protocol. Patients were seen by one rheumatologist (MP). A total of 2,228 SLE patients diagnosed according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria¹⁵ or the revised classification criteria as defined by the American College of Rheumatology (ACR)¹⁶ and as

updated in 1997¹⁷ and with at least three clinical visits were included in the analyses. At each clinic visit, the physician global disease activity on a 0–3 visual analog scale (PGA)¹⁸, the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE disease activity index (SELENA-SLEDAI)^{19, 20}, SLICC/ACR Damage Index (SDI)²¹, relevant serologies (anti-dsDNA, complement), and treatment were recorded.

In this study, we applied LLDAS⁵ to the Hopkins Lupus Cohort. LLDAS was defined as a SELENA-SLEDAI score of 4 with no scores for the renal, central nervous system, cardiopulmonary, vasculitis, fever, hemolytic anemia or gastrointestinal activity, no increase in any SELENA-SLEDAI component since the previous visit, a physician global assessment of 1, and a prednisone dose of 7.5 mg/day. Immunosuppressants and hydroxychloroquine treatment were allowed in the LLDAS definition.

Using the information collected, we applied the aforementioned definition of LLDAS to determine whether LLDAS was achieved at each visit for each patient. To identify the number of days in LLDAS between any two clinical visits, if a patient was in LLDAS at current visit, days of LLDAS were calculated as days from current visit to next visit. To calculate the percentage of time in LLDAS, the patient's total number of days in LLDAS was divided by the total number of days of follow up in the cohort. Follow up time that occurred after a gap of more than 7 months between clinic visits were excluded. LLDAS-50 was defined as being in LLDAS for at least 50% of the observation time. Patients were then classified into groups based on whether they had achieved LLDAS-50 or not.

Logistic regression was used to identify patient characteristics that were associated with LLDAS-50. We evaluated the relationship between each variable and LLDAS-50 one at a time. Those identified as possible factors from the univariate analyses ($p < 0.1$) were further analyzed. A multivariable logistic regression model in a backward stepwise elimination manner was used to determine independent predictors of LLDAS-50. Hosmer-Lemeshow goodness of fit statistics were used to assess the model fit.

Results

Patient Characteristics

This analysis included 2228 patients. 92.2% were female, 40% African-American and, 51.9% Caucasian. Fifty percent of the patients were diagnosed with SLE under the age of 30 years, 24.8% between the age of 30 and 40, 14.6% between 40 and 50, and 10.6% diagnosed at age of 50 and over. Cumulative classification criteria were 49% malar rash, 20% discoid rash, 52% photosensitivity, 53% oral ulcer, 72% arthritis, 50% serositis, 46% renal disorder, 12% neurological disorder, 69% hematological disorder, 83% immunological disorder and 97% ANA positivity based on the revised ACR classification criteria. Additional SLICC classification criteria included 21% direct Coombs test, 56% low C3, 48% low C4 and 17% low CH50. Mean follow up in the cohort was 8.9 ± 7.5 years. Mean SLE duration at the last visit was 14 ± 9.6 years.

Table 1 outlines the patient characteristics according to percentage of time in LLDAS, $< 50\%$ vs. $\geq 50\%$. Overall, 1169 (52.5%) of patients, but only 37.6% of African-Americans achieved

LLDAS-50. Patients who were older at diagnosis, more educated, were Caucasian, had private insurance, had longer disease duration, more percentage of time taking hydroxychloroquine, and accrued less damage during follow up were more likely to have achieved LLDAS-50. The likelihood of LLDAS-50 was similar by gender, smoking history, anticardiolipin antibody and lupus anticoagulant (by dRVVT with confirmatory testing) positivity. The proportion of LLDAS-50 was lower in patients with more percentage of time taking an immunosuppressant drug, low C3, low C4, anti-Sm, anti-RNP, and anti-dsDNA positivity.

Table 2 details the clinical manifestations. Patients with a history of, mucosal ulcer and livedoid rash were more likely to have achieved LLDAS-50. The likelihood of LLDAS-50 or not was similar in patients with a history of photosensitive rash, Raynaud's, subacute cutaneous lupus erythematosus (SCLE), bullous lupus, and panniculitis. Patients with a history of other clinical variables, including malar rash, discoid rash, alopecia, vasculitis, leg ulcers, arthritis, myositis, serositis, hematological and renal manifestations, were less likely to have achieved LLDAS-50.

Predictors of LLDAS-50

Table 3 shows the characteristics of patients that were associated with LLDAS-50 based on the multivariable logistic regression model. In the multivariable model, African-American ethnicity, anti-RNP, anti-dsDNA, low complement, history of serositis, vasculitis, renal activity, arthritis, malar rash, discoid rash, thrombocytopenia, and % of time taking an immunosuppressant drug remained negative predictors. Older age at diagnosis, longer disease duration, higher education level, and higher % of time taking hydroxychloroquine remained positive predictors of achieving LLDAS-50. Other covariates were not significant predictors of LLDAS-50, but included in the selection process were anti-Sm, photosensitive rash, mouth ulcers, alopecia, leg ulcers, livedo, myositis, coombs positivity, hemolytic anemia, leukopenia, and insurance.

Discussion

LLDAS-50 leads to less organ damage and mortality^{7, 14}. Understanding the predictive factors for ability or inability to achieve LLDAS-50 would lead to better clinical trial design and better clinical management of SLE patients. The current study was conducted in one of the largest SLE cohorts, and with a balanced representation of Caucasian and African-American ethnicities. We analyzed 2228 patients with a mean of 8.9 years follow up. This is the first study to define predictors of LLDAS-50. We took into account individual SLEDAI parameters and not just total SLEDAI, to determine clinical parameters that were associated with or prevented LLDAS-50.

First, over half of SLE patients in our cohort did achieve LLDAS-50. Franklyn *et al* found 38.2% of their Caucasian and Asian patients spent 50% of their 3.9 years follow up in LLDAS⁵. Noosent *et al* reported that 33.5% of their Caucasian patients were in LLDAS over 50% of the 125 months of follow up. The lower proportion of patients with LLDAS-50 in their studies may be due to the longer disease duration in our cohort, as SLE disease activity tends to decrease over time²². Tsang-A-Sjoe *et al* found 64.5% of their patients (68%

Caucasian) achieved LLDAS at 50% of their yearly visits during 5 years of follow up. However, their study was based on proportions of yearly visits, not overall time of follow up.

Second, one of the most important results, not previously studied, is that, compared to other ethnicities, African-Americans were significantly less likely to achieve LLDAS-50. Thirty-seven percent of African-American patients vs. 64% Caucasian were able to achieve LLDAS-50. African-Americans experience more severe SLE, and have a higher risk of lupus nephritis, discoid lupus, and hematologic, serologic, and immunologic SLE manifestations²³⁻³¹. Even after adjustment for education, insurance, clinical, serological and treatment variables, African-American ethnicity remained negatively associated with LLDAS-50. Our findings further emphasize the importance of inclusion of African-Americans in clinical trials.

Third, a higher percentage of time taking hydroxychloroquine was an independent modifiable predictor of LLDAS-50. This is a striking finding of this study, since it was the only modifiable predictor even after adjustment for demographics, disease characteristics and other therapeutics. Hydroxychloroquine (HCQ) has been recommended for all SLE patients irrespective of disease activity, unless contraindicated³². It has been shown to improve survival³³⁻³⁵, decrease frequency of lupus flares³⁶, and reduce risk of damage accrual³⁷. Yet poor adherence to treatment³⁸, misdiagnosis of HCQ related retinopathy, and under dosing due to concern of retinopathy are not uncommon. Adherence in both clinical practice and in randomized clinical trials is essential.

Fourth, immunosuppressant drug use was inversely associated with LLDAS-50. Immunosuppressant drug use was also found to be a negative predictor of two consecutive year in LLDAS⁶. Immunosuppressant drugs are recommended to SLE patients with frequent flares, unable to taper corticosteroids due to persistent disease activity, frequent flares, or severe organ involvement³², which means their use identifies a subset with more severe SLE. The fact that immunosuppressant drug use was a predictor of lack of LLDAS-50 is due to reverse causality: disease activity influences treatment decisions and vice versa. In this context, it would be more reasonable to accentuate other predictors found after adjustment for treatment rather than interpreting immunosuppressant drug use as a predictor.

As expected, the majority of SLE specific manifestations were less frequent in patients with LLDAS-50. However, patients with a history of mucosal ulcer and livedoid rash were more likely to achieve LLDAS-50. The proportion of LLDAS-50 was similar based on history of Raynaud's, photosensitive rash, subacute cutaneous lupus erythematosus, bullous lupus and panniculitis. In the final multivariable model, history of serositis, renal activity, arthritis, vasculitis, malar rash, discoid rash, and thrombocytopenia remained negative predictors of LLDAS-50. Two past studies reported predictors of duration in LLDAS^{6, 9}. Skin manifestations and arthritis were found to be negative predictors of both two and five consecutive years in LLDAS^{6, 9}. Serositis and vasculitis were found to be negative predictors only for two consecutive years in LLDAS⁶. These results are consistent with ours. Hematological manifestations other than thrombocytopenia, majority of skin manifestations, mouth ulcers, myositis, and anti-Sm were not found predictor of LLDAS-50 in our study.

Low complement, anti-dsDNA, and anti-RNP prevented LLDAS-50 in our study. Importantly, all of them are more common in African-American SLE^{26, 27, 29, 30, 39}, and associate with lupus nephritis^{39, 40}. Low C3 was an independent predictor of flares at week 52 in the post hoc analysis of belimumab trials⁴¹, and has been associated with poor survival⁴², and incident proteinuria⁴³. Contrast with anti-dsDNA⁴⁴, the relationship between disease activity and anti-extractable nuclear antigen (ENA) antibodies is still controversial⁴⁵. Anti-RNP associates with Raynaud's, leukopenia, and skin manifestations⁴⁶. However, anti-RNP as a negative predictor of LLDAS-50 persisted even after adjustment for anti-RNP associates, suggesting further connection between anti-RNP and prognosis.

Additional findings of this study are of interest. Longer disease duration and older age at diagnosis were associated with LLDAS-50. These results are in agreement with other studies. It is well established that SLE disease activity decreases over time²². Patients who were in LLDAS 50 of the observed time were found to be older at diagnosis^{5, 8}. Younger age at diagnosis was found to be negatively associated with LLDAS attainment in another study⁴⁷.

There are several limitations, including the single center and single rheumatologist in this study. Our cohort consists of mainly patients of Caucasian and African-American ethnicity, which did not allow us to investigate Asian-American and Hispanic-American lupus. We could not include prednisone dose in the analysis as it is a part of the LLDAS definition⁵.

In conclusion, in this large cohort, only 52.5% achieved LLDAS-50. This proportion was even less in African-Americans. A higher percentage of time taking hydroxychloroquine was a modifiable predictor of LLDAS-50. Low complement, anti-dsDNA, and anti-RNP were negative predictors. Our findings further emphasize the importance of inclusion of African-Americans in clinical trials and hydroxychloroquine adherence in both clinical practice and clinical trials.

Funding

The Hopkins Lupus Cohort was funded by the US National Institutes of Health: R01 AR 43727.

References

1. Barr SG, Zonana-Nacach A, Magder LS and Petri M. Patterns of disease activity in systemic lupus erythematosus. *Arthritis Rheum.* 1999; 42: 2682–8. [PubMed: 10616018]
2. Stoll T, Sutcliffe N, Mach J, Klaghofer R and Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus--a 5-yr prospective study. *Rheumatology (Oxford).* 2004; 43: 1039–44. [PubMed: 15161983]
3. Jorge AM, Lu N, Zhang Y, Rai SK and Choi HK. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999–2014). *Rheumatology (Oxford).* 2018; 57: 337–44. [PubMed: 29121273]
4. Wilhelm TR, Magder LS and Petri M. Response to: 'Remission in SLE: the duration depends on multiple factors, including the definition' by Doria et al. *Ann Rheum Dis.* 2016; 75: e78. [PubMed: 27797752]
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. [PubMed: 26458737]

6. 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. [PubMed: 28970217]
7. Petri M and 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. [PubMed: 29806142]
8. Tsang ASMW Bultink IE, Heslinga M and Voskuyl AE. 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. [PubMed: 27803306]
9. Tani C, Vagelli R, Stagnaro C, Carli L and Mosca M. Remission and low disease activity in systemic lupus erythematosus: an achievable goal even with fewer steroids? Real-life data from a monocentric cohort. *Lupus Sci Med*. 2018; 5: e000234. [PubMed: 29531772]
10. Golder V, Kandane-Rathnayake R, Hoi AY, 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: 62. [PubMed: 28320433]
11. Morand EF, Trasieva T, Berglind A, Illei GG and Tummala R. Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. *Ann Rheum Dis*. 2018; 77: 706–13. [PubMed: 29420200]
12. Oon S, Huq M, Golder V, Ong PX, Morand EF and Nikpour M. Lupus Low Disease Activity State (LLDAS) discriminates responders in the BLISS-52 and BLISS-76 phase III trials of belimumab in systemic lupus erythematosus. *Ann Rheum Dis*. 2019; 78: 629–33. [PubMed: 30679152]
13. Wallace DJ, Furie RA, Tanaka Y, de Bono S and Hoffman RW. Baricitinib for systemic lupus erythematosus - Authors' reply. *Lancet*. 2019; 393: 402–3.
14. Sharma C, Raymond W, Eilertsen G and 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 (Hoboken)*. 2019.
15. Petri M, Orbai AM, Alarcon 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. [PubMed: 22553077]
16. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982; 25: 1271–7. [PubMed: 7138600]
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997; 40: 1725.
18. Petri M, Hellmann D and Hochberg M. Validity and reliability of lupus activity measures in the routine clinic setting. *J Rheumatol*. 1992; 19: 53–9. [PubMed: 1556700]
19. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med*. 2005; 353: 2550–8. [PubMed: 16354891]
20. Bombardier C, Gladman DD, Urowitz MB, Caron D and Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992; 35: 630–40. [PubMed: 1599520]
21. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*. 1996; 39: 363–9. [PubMed: 8607884]
22. Zhang J, Gonzalez LA, Roseman JM, Vila LM, Reveille JD and Alarcon GS. Predictors of the rate of change in disease activity over time in LUMINA, a multiethnic US cohort of patients with systemic lupus erythematosus: LUMINA LXX. *Lupus*. 2010; 19: 727–33. [PubMed: 20118158]
23. Giannakou I, Chatzidionysiou K, Magder LS, Gyori N, van Vollenhoven R and Petri MA. Predictors of persistent disease activity and long quiescence in systemic lupus erythematosus: results from the Hopkins Lupus Cohort. *Lupus Sci Med*. 2018; 5: e000287. [PubMed: 30538818]
24. Carter EE, Barr SG and Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol*. 2016; 12: 605–20. [PubMed: 27558659]

25. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. *Arthritis Rheum.* 2013; 65: 753–63. [PubMed: 23203603]
26. Alarcon GS, Roseman J, Bartolucci AA, et al. Systemic lupus erythematosus in three ethnic groups: II. Features predictive of disease activity early in its course. LUMINA Study Group. *Lupus in minority populations, nature versus nurture.* *Arthritis Rheum.* 1998; 41: 1173–80. [PubMed: 9663472]
27. Alarcon GS, Friedman AW, Straaton KV, et al. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. *LUpus in MINority populations: NAture vs. Nurture.* *Lupus.* 1999; 8: 197–209. [PubMed: 10342712]
28. Krishnan E and Hubert HB. Ethnicity and mortality from systemic lupus erythematosus in the US. *Ann Rheum Dis.* 2006; 65: 1500–5. [PubMed: 16627544]
29. Ward MM and Studenski S. Clinical manifestations of systemic lupus erythematosus. Identification of racial and socioeconomic influences. *Arch Intern Med.* 1990; 150: 849–53. [PubMed: 2327845]
30. Cooper GS, Parks CG, Treadwell EL, et al. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. *Lupus.* 2002; 11: 161–7. [PubMed: 11999880]
31. Alarcon GS, McGwin G Jr., Petri M, et al. Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus.* 2002; 11: 95–101. [PubMed: 11958584]
32. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019; 78: 736–45. [PubMed: 30926722]
33. Alarcon GS, McGwin G, Bertoli AM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis.* 2007; 66: 1168–72. [PubMed: 17389655]
34. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus.* 2006; 15: 577–83. [PubMed: 17080912]
35. Mok CC, Tse SM, Chan KL and Ho LY. Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. *Lupus.* 2018; 27: 722–7. [PubMed: 29087260]
36. Canadian Hydroxychloroquine Study G A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med.* 1991; 324: 150–4. [PubMed: 1984192]
37. Fessler BJ, Alarcon GS, McGwin G Jr., et al. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum.* 2005; 52: 1473–80. [PubMed: 15880829]
38. Durcan L, Clarke WA, Magder LS and Petri M. Hydroxychloroquine Blood Levels in Systemic Lupus Erythematosus: Clarifying Dosing Controversies and Improving Adherence. *J Rheumatol.* 2015; 42: 2092–7. [PubMed: 26428205]
39. Bastian HM, Roseman JM, McGwin G Jr., et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus.* 2002; 11: 152–60. [PubMed: 12004788]
40. Petri M Hopkins Lupus Cohort. 1999 update. *Rheum Dis Clin North Am.* 2000; 26: 199–213, v. [PubMed: 10768209]
41. Petri MA, van Vollenhoven RF, Buyon J, et al. Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III belimumab trials. *Arthritis Rheum.* 2013; 65: 2143–53. [PubMed: 23754628]
42. Kasitanon N, Magder LS and Petri M. Predictors of survival in systemic lupus erythematosus. *Medicine (Baltimore).* 2006; 85: 147–56. [PubMed: 16721257]
43. Duarte-Garcia A, Barr E, Magder LS and Petri M. Predictors of incident proteinuria among patients with SLE. *Lupus Sci Med.* 2017; 4: e000200. [PubMed: 29177060]
44. ter Borg EJ, Horst G, Hummel EJ, Limburg PC and Kallenberg CG. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus

- erythematosus. A long-term, prospective study. *Arthritis Rheum.* 1990; 33: 634–43. [PubMed: 2346519]
45. Kattah NH, Kattah MG and Utz PJ. The U1-snRNP complex: structural properties relating to autoimmune pathogenesis in rheumatic diseases. *Immunol Rev.* 2010; 233: 126–45. [PubMed: 20192997]
46. Tang X, Huang Y, Deng W, Tang L, Weng W and Zhang X. Clinical and serologic correlations and autoantibody clusters in systemic lupus erythematosus: a retrospective review of 917 patients in South China. *Medicine (Baltimore).* 2010; 89: 62–7. [PubMed: 20075706]
47. Golder V, Kandane-Rathnayake R, Hoi AY, et al. Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort. *Arthritis Res Ther.* 2016; 18: 260. [PubMed: 27829463]

Table 1.

Prevalence of patients achieving LLDAS at least 50% of their observation time by patient demographics and laboratory markers

	Proportion (%) with LLDAS 50%	Odds ratio (95% CI)	p-value
Sex			
Female	1080/2054 (52.6%)	Ref	
Male	89/174 (51.2%)	0.94 (0.69, 1.29)	0.7164
Ethnicity			
Caucasian	743/1157 (64.2%)	Ref	
African-American	335/892 (37.6%)	0.34 (0.28, 0.40)	<0.0001
Other	91/179 (50.8%)	0.58, 0.42, 0.79)	0.0006
Age at diagnosis, years			
<30	503/1114 (45.2%)	Ref	
30–39	294/551 (53.4%)	1.39 (1.13, 1.71)	0.0016
40–49	215/324 (66.4%)	2.4 (1.85, 3.1)	<0.0001
50	157/237 (66.2%)	2.38 (1.78, 3.2)	<0.0001
Education			
Below High-School	83/203 (40.9%)	Ref	
High School	258/539 (47.9%)	1.33 (0.96, 1.84)	0.0894
Some College	316/606 (52.2%)	1.58 (1.14, 2.17)	0.0057
College Graduate	492/829 (59.4%)	2.11 (1.55, 2.88)	<0.0001
Insurance			
None	18/54 (33.3%)	Ref	
MA	174/419 (41.5%)	1.42 (0.78, 2.58)	0.2504
Private	961/1709 (56.2%)	2.57 (1.45, 4.56)	0.0013
History of smoking			
Never	744/1408 (52.8%)	Ref	
Ever	420/809 (51.9%)	0.96 (0.81, 1.15)	0.6746
Duration of SLE (at last visit)			
1–5 years	200/436 (45.9%)	Ref	
5–10 years	241/463 (52.1%)	1.28 (0.99, 1.67)	0.0641
10–20 years	412/781 (52.8%)	1.32 (1.04, 1.67)	0.0215
20+ years	316/546 (57.9%)	1.62 (1.26, 2.09)	0.0002
Percentage of time taking hydroxychloroquine			
<50%	278/638 (43.6%)	Ref	
50%	891/1590 (56%)	1.65 (1.37, 1.99)	<0.0001
Percentage of time taking immunosuppressant			
<50%	931/1479 (63%)	Ref	
50%	238/749 (31.8%)	0.27 (0.23, 0.33)	<0.0001
Low C3			
Never	649/971 (66.8%)		
Ever	519/1255 (41.4%)	0.35 (0.29, 0.42)	<0.0001

	Proportion (%) with LLDAS 50%	Odds ratio (95% CI)	p-value
Low C4			
Never	738/1151 (64.1%)		
Ever	430/1075 (40%)	0.37 (0.31, 0.44)	<0.0001
Anti-Sm			
Never	987/1713 (57.6%)		
Ever	164/470 (34.9%)	0.39 (0.32, 0.49)	<0.0001
Anti-RNP			
Never	913/1533 (59.6%)		
Ever	240/644 (37.3%)	0.4 (0.33, 0.49)	<0.0001
Anti-dsDNA			
Never	537/817 (65.7%)		
Ever	629/1407 (44.7%)	0.42 (0.35, 0.5)	<0.0001
Anticardiolipin			
Never	579/1113 (52%)		
Ever	569/1063 (53.5%)	1.06 (0.9, 1.26)	0.4818
Lupus anticoagulant			
Never	839/1588 (52.8%)		
Ever	313/590 (53.1%)	1.01 (0.83, 1.22)	0.9281
Damage accrual during follow up			
SDI 1	808/1444 (56%)		
SDI >1	354/769 (46%)	0.67 (0.56, 0.8)	<0.0001

Table 2.

Prevalence of patients achieving LLDAS at least 50% of their observation time by clinical manifestations

Ever clinical manifestations	Proportion (%) of patient with LLDAS 50% of observation time		Odds ratio (95% CI)	p-value
	With disease manifestation	Without disease manifestation		
Cutaneous activity	1115/2119 (52.6%)	54/107 (50.5%)	1.09 (0.74, 1.61)	0.6637
Malar Rash	547/1090 (50.2%)	621/1136 (54.7%)	0.84 (0.71, 0.99)	0.0343
Discoid	186/444 (41.9%)	983/1780 (55.2%)	0.58 (0.47, 0.72)	<0.0001
Photosensitive rash	631/1162 (54.3%)	538/1064 (50.6%)	1.16 (0.98, 1.37)	0.0777
Mucosal Ulcer	650/1181 (55%)	519/1045 (49.7%)	1.24 (1.05, 1.47)	0.0113
Alopecia	605/1266 (47.8%)	564/959 (58.8%)	0.64 (0.54, 0.76)	<0.0001
Raynaud's	592/1156 (51.2%)	576/1068 (53.9%)	0.9 (0.76, 1.06)	0.1992
Subacute cutaneous lupus	59/118 (50%)	1110/2106 (52.7%)	0.9 (0.62, 1.3)	0.5668
Bullous lupus	7/17 (41.2%)	1154/2183 (52.9%)	0.62 (0.24, 1.65)	0.3407
Vasculitis	126/329 (38.3%)	1043/1896 (55%)	0.51 (0.4, 0.65)	<0.0001
Livedoid Rash	344/584 (58.9%)	824/1639 (50.3%)	1.42 (1.17, 1.72)	0.0003
Leg ulcers	17/57 (29.8%)	1152/2168 (53.1%)	0.37 (0.21, 0.67)	0.0008
Panniculitis	23/52 (44.2%)	1146/2172 (52.8%)	0.71 (0.41, 1.24)	0.2255
Musculoskeletal activity	819/1643 (49.9%)	347/576 (60.2%)	0.66 (0.54, 0.8)	<0.0001
Arthritis	803/1607 (50%)	363/613 (59.2%)	0.69 (0.57, 0.83)	0.0001
Myositis	68/178 (38.2%)	1097/2041 (53.8%)	0.53 (0.39, 0.73)	0.0001
Renal activity	507/1252 (40.5%)	657/966 (68%)	0.32 (0.27, 0.38)	<0.0001
Proteinuria	363/1025 (35.4%)	803/1196 (67.1%)	0.27 (0.23, 0.32)	<0.0001
Nephrotic Syndrome	112/413 (27.1%)	1050/1788 (58.7%)	0.26 (0.21, 0.33)	<0.0001
Hematuria	221/635 (34.8%)	941/1577 (59.7%)	0.36 (0.3, 0.44)	<0.0001
Renal Insufficiency	256/670 (38.2%)	911/1553 (58.7%)	0.44 (0.36, 0.52)	<0.0001
Renal Failure	47/173 (27.2%)	1116/2040 (54.7%)	0.31 (0.22, 0.44)	<0.0001
Hematological activity	668/1391 (48%)	420/666 (63.1%)	0.54 (0.45, 0.65)	<0.0001
Coombs	154/404 (38.1%)	880/1507 (58.4%)	0.44 (0.35, 0.55)	<0.0001
Hemolytic Anemia	85/231 (36.8%)	1046/1921 (54.5%)	0.49 (0.37, 0.65)	<0.0001
Thrombocytopenia	201/467 (43%)	966/1756 (55%)	0.62 (0.5, 0.76)	<0.0001
Leukopenia	507/1066 (47.6%)	662/1158 (57.2%)	0.68 (0.57, 0.8)	<0.0001
Serositis activity	477/1101 (43.3%)	690/1124 (61.4%)	0.48 (0.41, 0.57)	<0.0001

OR in interpreted as the odds of LLDAS-50 in patients with manifestation compared those patients without manifestation.

Table 3.

Multivariable logistic regression of the association between LLDAS-50 and patient characteristics

	Odds ratio (95% CI)	p-value
Ethnicity		
Caucasian	Ref	
African American	0.41 (0.33, 0.52)	<.0001
Other	1.01 (0.68, 1.49)	0.9653
Education status		
Below high school	Ref	
High school	1.26 (0.85, 1.87)	0.2427
Some college	1.47 (0.99, 2.18)	0.0536
College	1.79 (1.22, 2.62)	0.0032
History of hypocomplementemia	0.6 (0.47, 0.75)	<.0001
History of serositis	0.59 (0.48, 0.72)	<.0001
History of renal activity	0.55 (0.44, 0.68)	<.0001
History of arthritis	0.7 (0.55, 0.89)	0.0036
History of anti-RNP positivity	0.69 (0.55, 0.87)	0.002
History of anti-dsDNA	0.74 (0.59, 0.93)	0.0092
History of vasculitis	0.63 (0.47, 0.84)	0.002
History of malar rash	0.78 (0.63, 0.97)	0.0263
History of discoid rash	0.71 (0.54, 0.92)	0.0105
History of thrombocytopenia	0.73 (0.57, 0.94)	0.016
Proportion of time taking immunosuppressants (per unit difference)	0.27 (0.2, 0.35)	<.0001
Proportion of time taking hydroxychloroquine (per unit difference)	2.21 (1.69, 2.89)	<.0001
Age at diagnosis (per year difference)	1.02 (1.01, 1.03)	<.0001
SLE duration at last visit (per year difference)	1.06 (1.04, 1.07)	<.0001

Other covariates that were not significantly predictive of over 50% of time in LLDAS but included in the selection process were anti-Sm, photosensitive rash, mouth ulcers, alopecia, leg ulcers, livedo, myositis, coombs, leukopenia, and hemolytic anemia