

Frequency and predictors of the Lupus Low Disease Activity State in Chinese patients with systemic lupus erythematosus: a prospective observational cohort study

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Abstract

Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with significant risk of organ damage. Lupus Low Disease Activity State (LLDAS) was generated as a potential treatment target for SLE. Previous studies had validated that the maintenance of LLDAS can predict reduced damage accrual or flare. The objective of this study was to estimate the time to LLDAS and the predictors of time to LLDAS in our prospective observational cohort of Chinese patients with SLE.

Methods Patients were from Peking University First Hospital SLE cohort and those having not fulfilled LLDAS at enrolment were included in this study. The time to LLDAS and annual cumulative probabilities of LLDAS achievement were estimated by the Kaplan-Meier approach. The predictors of time to LLDAS were identified by univariate and multivariable Cox proportional hazards.

Results A total of 574 patients with SLE were included and 435 (75.8%) of them achieved LLDAS during a median 4.2 years of follow-up. The median time to LLDAS was 19.0 months and the cumulative probabilities at 1, 2, 3, 5 and 10 years were 19.8%, 57.6%, 72.0%, 85.1% and 98.0%, respectively. In multivariable Cox models, older age at disease onset, treatment-naïve and hydroxychloroquine prescription were found to be independent predictors of shorter time to LLDAS, after adjusted by daily prednisone dose, SLE Disease Activity Index 2000 and physician's global assessment. Finally, we developed a matrix model based on the identified independent predictors to present the time to LLDAS in patients with respective characteristics.

Conclusions Our study proved that LLDAS is attainable as an early treatment target for SLE in Chinese patients. The older age at disease onset, treatment-naïve and hydroxychloroquine prescription were independent predictors of shorter time to LLDAS.

Background

Systemic lupus erythematosus (SLE) is a challenging chronic autoimmune disorder with variable clinical manifestations. The survival rate of patients with SLE has got progressive improvement with early diagnosis and pharmacopoeia development over the past decades; however, the mortality of SLE is still twice of the general population [1–4].

Long-term observational studies have demonstrated that disease activity was positively associated with the risk of subsequent organ damage and mortality [5, 6]. In accordance with these findings, remission and the lowest possible disease activity were set as the treatment targets of SLE in the treat-to-target recommendations released in 2014 [7].

Recently, a framework for remission in SLE has been established by a large international task force, however, the framework contained four different definitions and no specific definition of remission has been widely accepted by now [8]. Furthermore, the attainability and sustainability of these definitions were still in debate [9–13].

In contrast with remission, low disease activity state was more appropriate as an early treatment target with higher attainability and sustainability [12–19]. Among the definitions of low disease activity in SLE, the Lupus Low Disease Activity State (LLDAS) developed by Asia-Pacific Lupus Collaboration was well-validated and widely accepted [9–11, 20–22]. Previous studies had proved that the maintenance of LLDAS during follow-up was associated with a lower frequency of organ damage accrual or flare [14–16, 22–25]. Meanwhile, some studies had revealed the associated factors of maintaining LLDAS during follow-up [14, 15, 22–26]. However, most of these studies included the patients who had already achieved LLDAS at baseline, therefore, they were unable to analyse the attainability of LLDAS achievement from high or moderate disease activity to LLDAS.

Until now, the only one study which estimated the attainability of LLDAS was the Hopkins Lupus Cohort study consisting of Caucasian and African-American SLE patients [26]. Several studies found that Asians had significant differences with Caucasians in terms of disease activity, renal involvement, autoantibody-positive rate, organ damage rate and mortality rate [27–32]. Moreover, studies by Asia-Pacific Lupus Collaboration showed that the possibility of LLDAS \geq 50% time during follow-up was lower in Asian population than that in Caucasians, though it did not reach statistical difference [22, 23]. No data about the attainability of LLDAS achievement in Asian ethnicity has been reported so far.

In this study, we estimated the time to LLDAS and the predictors of time to LLDAS in our prospective observational cohort of Chinese patients with SLE.

Methods

Patients

The Peking University First Hospital SLE (PKUFHS) cohort is a single-centre prospective observational cohort since 2007. Patients were diagnosed according to the revised American College of Rheumatology (ACR) criteria or the Systemic Lupus International Collaborating Clinics (SLICC) criteria. After the recruitment, patients were regularly followed up every 1 to 3 months when the disease was active, or every 3 to 6 months when the disease was stable, which was determined by the rheumatologists.

In this study, patients from the PKUFHS cohort recruited between January 2007 and December 2018 were included if they meet all of the following criteria: (a) did not fulfil LLDAS at baseline; (b) had no other connective tissue diseases except Sjogren's syndrome (SS) or antiphospholipid syndrome (APS), inflammatory arthropathy or other diseases exerting obvious effect on disease activity assessment and GCs tapering; (c) had at least 3 follow-up visits and 6 months of follow-up duration; and (d) had no interval of more than 12 months between two consecutive visits.

This study was approved by the ethics committee of Peking University First Hospital and all patients signed the informed consent at enrolment.

Data collection

Data were collected at outpatient visits and hospital admissions from January 2007 to June 2019. Gender, age at disease onset and disease duration were recorded with baseline manifestations, laboratories and complications, including SS and APS.

Age at disease onset was defined as the age when the symptom or laboratory abnormality related to SLE was initially presented. Disease duration was defined as the time from disease onset to the recruitment. Early SLE was defined when the disease duration was no more than 1 year. Treatment-naïve was defined as no previous glucocorticoid or immunosuppressants (IMs) therapy. Clinical manifestations and laboratories were defined and recorded with the reference of the SLE Disease Activity Index 2000 (SLEDAI-2K) [33, 34]. Additionally, nephritis was defined when either of proteinuria, haematuria, sterile pyuria or urinary casts was presented. Serositis was defined as pleurisy or pericarditis. Anaemia was defined when the haemoglobin was less than 12 g/dl in women and 13 g/dl in men according to the WHO definition [35].

The disease activity of SLE was assessed by 1 rheumatologist using the SLEDAI-2K and the physician's global assessment (PGA) (range 0–3.0) at baseline and each visit [33, 36]. Organ damage of each patient was determined by the SLICC/ACR Damage Index (SDI) at baseline [37]. The daily prednisone (or equivalent) dose, and hydroxychloroquine (HCQ) and IMs usage at baseline and each visit were also collected.

LLDAS

The definitions of LLDAS were: (a) SLEDAI-2K ≤ 4 , with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever), and no haemolytic anaemia or gastrointestinal active; (b) No new features of lupus disease activity compared with the previous assessment; (c) PGA ≤ 1 ; (d) Prednisone dose ≤ 7.5 mg/day; and (e) Well-tolerated standard maintenance doses of IMs [22]. The time to LLDAS was defined as the duration from baseline to the first follow-up visit achieving LLDAS.

Statistical analysis

Descriptive statistics were presented as the median (interquartile range (IQR) (25th percentile–75th percentile)) for continuous variables and numbers (frequency or percentages) for categorical variables. The Mann–Whitney U test was performed for continuous variables and the chi-squared test was performed for categorical variables. The Kaplan-Meier curve was used to estimate the median (IQR) time to LLDAS and the annual cumulative probabilities of LLDAS achievement. Univariate and multivariable Cox proportional hazards model were used to identify predictors of time to LLDAS. Factors with p-value ≤ 0.1 on univariate analysis then entered into the multivariate model and those that remained significant were retained in the models. The components of LLDAS (daily prednisone dose, SLEDAI and PGA) were added into the model for adjustment after performing the initial multivariate analysis. Finally, we investigated the baseline predictors of time to LLDAS and constructed a matrix model based on the identified independent predictors to present the time to LLDAS in patients with different characteristics at

baseline. For better illustration, categorical variables would be converted to two-category or multiple-category variables.

All analyses were performed with STATA version 15.1 (StataCorp, College Station, TX, USA) for Windows and a p-value of <0.05 was considered statistically significant.

Results

Demographics and baseline characteristics

The baseline characteristics of 574 patients with SLE included in this study were shown in Table 1. In these patients, 491 (85.5%) were female and the median (IQR) age at onset was 28.8 (21.7-38.7) years. In these patients, 206 (35.9%) had disease duration ≤ 1 year and 229 (39.9%) were treatment-naïve. The median (IQR) SLEDAI-2K and PGA at baseline were 8 (5-16) and 1.6 (1.0-1.9), respectively. At baseline, the median (IQR) daily prednisone (or equivalent) dose was 50 (30-60) mg and 394 (68.9%) patients received IMs.

LLDAS achievement

Patients were followed for a median (IQR) of 3.9 (2.1-6.5) years and 13 (9-20) visits. During follow-up, 435 (75.8%) patients achieved LLDAS at least once. The baseline characteristics and the comparison between patients who achieved and did not achieve LLDAS during follow-up were shown in Table 1. The patients who achieved LLDAS had younger age at disease onset ($p=0.027$), shorter disease duration ($p=0.004$), higher frequency of treatment-naïve ($p<0.001$), lower frequency of nephritis ($p=0.005$), lower SDI ($p=0.004$), less IMs usage ($p=0.005$), and lower level of SLEDAI ($p<0.001$) and PGA ($p=0.010$) at baseline compared with those who never achieved LLDAS during follow up.

The median (IQR) time to LLDAS was 20.5 (13.2, 40.2) months and the cumulative probabilities of achieving LLDAS at 1, 2, 3, 5 and 10 follow-up years were 19.8%, 57.6%, 72.0%, 85.1% and 98.0%, respectively. The Kaplan-Meier curve for time to LLDAS was illustrated in Figure 1.

Predictors of time to LLDAS

The predictors at baseline of time to LLDAS were identified by the univariable and multivariable Cox regression analyses.

In univariable analysis, baseline variables including male, age at disease onset, early SLE, treatment-naïve, complicating with SS, arthritis and HCQ prescription were positively associated with LLDAS achievement, while nephritis, serositis and hypocomplementemia, high SLEDAI, PGA and SDI, as well as IMs prescription were negatively associated with LLDAS achievement (Table 2).

In multivariable Cox regression analysis, older age at disease onset (HR 1.010, $p=0.005$), treatment-naïve (HR 1.346, $p=0.003$) and HCQ prescription at baseline (HR 1.638, $p<0.001$) were identified as positive

predictors of achieving LLDAS, while nephritis at baseline (HR 0.766, $p=0.009$) was detected as a negative predictor of LLDAS achievement (Table 3, model 1). The older age at disease onset, treatment-naïve and HCQ prescription remained significantly associated with a shorter time to LLDAS after adjusted by daily prednisone dose, SLEDAI and PGA. Moreover, high SLEDAI and PGA were negatively associated with a longer time to LLDAS (Table 3, model 2 and model 3).

Matrix model

Finally, we constructed a matrix model for time to LLDAS based on the identified independent factors associated with time to LLDAS, including age at disease onset, treatment-naïve and PGA (Figure 2). The numbers in each cell of the matrix model represented the median (IQR) time to LLDAS of patients with respective characteristics. For example, the median (IQR) time to LLDAS was 18.0 (13.0-32.9) months for treatment-naïve patients with age ≤ 30 years at disease onset and PGA 1.1-2.0 at baseline.

Discussions

This is the first study to estimate the time to LLDAS and the predictors of time to LLDAS in the Asian population. Furthermore, we used a matrix model to illustrate the time to LLDAS in patients with different baseline characteristics, aiming to provide references to the future clinical trials and the clinical practice.

This study demonstrated that LLDAS is attainable as a treatment target for Chinese patients with SLE. In our SLE cohort, the time to LLDAS was 1.7 years, which was longer than that in the Johns Hopkins Lupus Cohort (1.1 years) mainly consisting of Caucasian and African-American patients [26]. The difference may be partly due to the different disease activity at baseline. In their cohort, 50.7% of patients had PGA ≤ 1 and 53.8% had SLEDAI ≤ 4 at baseline, while the percentages in our patients were only 28.7% and 24.0%, respectively.

Our study confirmed that baseline disease activity could strongly influence the LLDAS achievement. Some previous studies found that patients with LLDAS $\geq 50\%$ of follow-up time had a lower level of SLEDAI at baseline [14, 22, 23], and other studies found that baseline SLEDAI ≤ 4 was a predictor of achieving LLDAS and maintaining LLDAS for 5 years [15, 26]. The present study showed that patients with lower disease activity (by PGA or SLEDAI-2K) at baseline were more quickly to achieve LLDAS. Particularly, some components of SLEDAI including active nephritis, serositis and hypocomplementemia were found to be predictors of achieving LLDAS with longer time, while arthritis was found to be predictors of earlier LLDAS achievement.

Our study indicated that the age at disease onset of SLE could influence the LLDAS achievement. Previous researches had demonstrated that patients with juvenile-onset SLE had higher disease activity, received more intensive prednisone and IMs therapy, had more organ damage and a two-fold higher mortality rate, compared with adult-onset patients [38-42]. Recently, some studies reported that patients who were in LLDAS $\geq 50\%$ time or observations during follow-up had older age at diagnosis of SLE [14,

22, 23]. In the present study, patients with older age at disease onset were demonstrated to have shorter time to LLDAS after adjusting other factors, including daily prednisone dose, SLEDAI and PGA.

It should be noted that early treatment was a strong positive predictor for LLDAS achievement. Babaoglu et al found that patients with disease duration ≤ 1 year had shorter time to LLDAS [26]. Our study confirmed the association and further found that treatment-naïve was also a positive predictor of LLDAS achievement. Moreover, patients with organ damage before recruitment were found to require longer time to achieve LLDAS. These evidences indicated early treatment could provide more opportunities for quick achievement of LLDAS.

Our study revealed that the patients who received HCQ as an initial treatment were able to achieve LLDAS faster. HCQ has been used in SLE for over half a century. Increasing evidences have been emerging to suggest the beneficial effects of HCQ, including reducing prednisone dose, decreasing disease activity, preventing lupus flares and organ damage accrual, and improving survival rate [43-49]. Babaoglu et al found that patients who received HCQ at baseline had a shorter time to LLDAS in univariable Cox model [26]. Our study further demonstrated that HCQ prescription was a strong independent predictor of shorter time to LLDAS, even after adjusted by disease activity factors. Apart from HCQ, other treatments were also evaluated in the present study. We found that those patients who used IMs at baseline required longer time to achieve LLDAS. A study from Tsang et al also showed that patients using IMs at baseline had a lower possibility of maintaining LLDAS $\geq 50\%$ time during follow-up [14].

We found that complicating SS in SLE patients predicted a shorter time to LLDAS. A study by Baer et al showed that patients with both SLE and SS were a distinct subset with older age at SLE diagnosis and lower frequency of renal involvement [50], and our study revealed this overlap was also a factor of earlier achievement of LLDAS.

There were some limitations in this study. As an observational study, our data can hardly be used to evaluate the effect of different IMs on achieving LLDAS in SLE. Data from prospective intervention studies were needed to determine which medication could help to achieve LLDAS with less time. In addition, as all of the patients in this cohort were Chinese ethnicity, the conclusions may not be extrapolated to other ethnicities.

Conclusions

Our study proved that LLDAS is attainable as an early treatment target for SLE in Chinese patients. Older age at disease onset, treatment-naïve, lower disease activity and HCQ prescription at baseline are predictors of earlier LLDAS achievement.

Abbreviations

ACR: American College of Rheumatology; anti-dsDNA: anti-double stranded DNA; APS: antiphospholipid syndrome; HCQ: hydroxychloroquine; IM: immunosuppressant; IQR: interquartile range; LLDAS: Lupus

Low Disease Activity State; PGA: physician's global assessment; PKUFHS: Peking University First Hospital SLE; SDI: SLICC/ACR Damage Index; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; SLICC: Systemic Lupus International Collaborating Clinics; SS: Sjogren's syndrome.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking University First Hospital (number: PKUFH-2017[1284]) and informed consent was obtained from each patient at enrolment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

Zhuoli Zhang and Yanjie Hao contributed to the design of the cohort and this study, and reviewed and revised the manuscript. Dai Gao contributed to the design of the study, to the collection, analysis and interpretation of the data, and drafted the manuscript. Lin Mu, Wenhui Xie, Yong Fan and Lanlan Ji contributed to the process of the data collection. All authors approved the final version of the manuscript and gave their agreement to the publication.

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Tables

Table 1 Baseline characteristics and comparisons of patients who achieved or not achieved LLDAS during follow-up

Characteristics	Overall	Achieved LLDAS	Not achieved LLDAS	<i>p</i> value*
	n=574	n=435	n=139	
Female	491 (85.5)	376 (86.4)	115 (82.7)	0.280
Age at disease onset, years	28.8 (21.7-38.7)	29.2 (22.3-39.8)	26.4 (20.3-36.3)	0.027
Disease duration, years	2.0 (0.4-6.1)	1.8 (0.3-5.5)	3.0 (0.7-8.1)	0.004
Treatment-naïve	229 (39.9)	192 (44.1)	37 (26.6)	<0.001
Comorbidities				
Sjogren's syndrome	127 (22.1)	103 (23.7)	24 (17.3)	0.113
Antiphospholipid syndrome	58 (10.1)	44 (10.1)	14 (10.1)	0.988
Clinical manifestations				
Fever	77 (13.4)	58 (13.3)	19 (13.7)	0.919
Mucosal ulcers	55 (9.6)	43 (9.9)	12 (8.6)	0.662
Alopecia	126 (22.0)	93 (21.4)	33 (23.7)	0.558
Rash	223 (38.9)	160 (36.8)	63 (45.3)	0.072
Raynaud's phenomenon	101 (17.6)	77 (17.7)	24 (17.3)	0.907
Arthritis	78 (13.6)	64 (14.7)	14 (10.1)	0.165
Myositis	15 (2.6)	10 (2.3)	5 (3.6)	0.404
Serositis	111 (19.3)	77 (17.7)	34 (24.5)	0.079
Neuropsychiatric manifestations	39 (6.8)	27 (6.2)	12 (8.6)	0.322
Nephritis	271 (47.2)	191 (43.9)	80 (57.6)	0.005
Haemolytic anaemia	26 (4.5)	20 (4.6)	6 (4.3)	0.890
Gastrointestinal involvement	26 (4.5)	17 (3.9)	9 (6.5)	0.205
Laboratory tests				
Anti-dsDNA positive	429 (74.7)	323 (74.3)	106 (76.3)	0.636
Hypocomplementemia	391 (68.1)	290 (66.7)	101 (72.7)	0.187
Proteinuria	233 (40.6)	160 (36.8)	83 (52.5)	0.001
Haematuria	181 (31.5)	126 (29.0)	55 (39.6)	0.019

Sterile pyuria	126 (22.0)	73 (16.8)	53 (38.1)	<0.001
Urinary casts	81 (14.1)	55 (12.6)	26 (18.7)	0.074
Anaemia	297 (51.7)	220 (50.6)	77 (55.4)	0.322
Leukopenia	129 (22.5)	104 (23.9)	25 (18.0)	0.145
Thrombocytopenia	108 (18.8)	80 (18.4)	28 (20.1)	0.645
Scores				
SLEDAI	8 (5-16)	8 (4-16)	11 (6-20)	<0.001
PGA	1.6 (1.0-1.9)	1.6 (0.9-1.8)	1.6 (1.2-2.2)	0.010
SDI	0 (0-2)	0 (0-1)	1 (0-2)	0.004
Treatments				
Daily prednisone (or equivalent) dose	50 (30-60)	50 (30-60)	45 (20-60)	0.929
HCQ	473 (82.4)	362 (83.2)	111 (79.9)	0.365
Immunosuppressants	395 (68.8)	286 (65.7)	109 (78.4)	0.005
Cyclophosphamide	134 (23.3)	96 (22.1)	38 (27.3)	0.201
Mycophenolate mofetil	122 (21.3)	83 (19.1)	39 (28.1)	0.024
Methotrexate	58 (10.1)	45 (10.3)	13 (9.4)	0.735
Azathioprine	46 (8.0)	33 (7.6)	13 (9.4)	0.504
Leflunomide	35 (6.1)	27 (6.2)	8 (5.8)	0.846
Cyclosporine A	17 (3.0)	15 (3.4)	2 (1.4)	0.224

Values in the table are median (interquartile range: 25th-75th) or number (%).

LLDAS Lupus Low Disease Activity State, *SLEDAI-2K* Systemic Lupus Erythematosus Disease Activity Index 2000, *PGA* physician's global assessment, *SDI* Systemic Lupus International Collaborating Clinics/ACR Damage Index, *anti-dsDNA* anti-double stranded DNA, *HCQ* hydroxychloroquine.

*Mann-Whitney U test for continuous variables, and chi-squared test for categorical variables. Numbers in bold font indicate statistical significance for $p < 0.05$.

Table 2 Baseline variables associated with LLDAS achievement based on univariable Cox model

Characteristics	HR (95% CI)	<i>p</i> value*
Female	0.728 (0.552-0.959)	0.024
Age at disease onset, years	1.011 (1.005-1.018)	0.001
Early SLE (disease duration ≤1 year)	1.401 (1.154-1.702)	0.001
Treatment-naïve	1.505 (1.243-1.823)	<0.001
Comorbidities		
Sjogren's syndrome	1.401 (1.121-1.750)	0.003
Antiphospholipid syndrome	0.871 (0.637-1.189)	0.384
Clinical manifestations		
Fever	1.031 (0.782-1.360)	0.829
Mucosal ulcers	1.217 (0.888-1.667)	0.223
Alopecia	1.025 (0.815-1.290)	0.831
Rash	0.959 (0.788-1.165)	0.671
Raynaud's phenomenon	0.883 (0.690-1.130)	0.324
Arthritis	1.400 (1.072-1.828)	0.013
Myositis	0.832 (0.444-1.558)	0.566
Serositis	0.764 (0.597-0.978)	0.033
Neuropsychiatric manifestations	0.736 (0.498-1.087)	0.124
Nephritis	0.741 (0.613-0.896)	0.002
Haemolytic anaemia	1.031 (0.658-1.616)	0.894
Gastrointestinal involvement	0.685 (0.421-1.116)	0.129
Laboratory tests		
Anti-dsDNA positive	0.907 (0.732-1.126)	0.377
Hypocomplementemia	0.830 (0.680-1.014)	0.068
Proteinuria	0.694 (0.571-0.845)	<0.001
Haematuria	0.796 (0.647-0.980)	0.032
Sterile pyuria	0.558 (0.433-0.718)	<0.001
Urinary casts	0.722 (0.544-0.959)	0.025
Anaemia	0.929 (0.769-1.122)	0.444

Leukopenia	1.137 (0.911-1.420)	0.256
Thrombocytopenia	0.923 (0.723-1.178)	0.520
Scores		
SLEDAI	0.979 (0.968-0.991)	<0.001
PGA	0.833 (0.730-0.952)	0.007
SDI	0.884 (0.816-0.959)	0.003
Treatments		
Daily prednisone (or equivalent) dose, mg/d	0.998 (0.995-1.002)	0.389
HCQ	1.734 (1.342-2.241)	<0.001
Immunosuppressants	0.726 (0.595-0.885)	0.002

LLDAS Lupus Low Disease Activity State, *HR* hazard ratio, *CI* confidence interval, *SLEDAI-2K* Systemic Lupus Erythematosus Disease Activity Index 2000, *PGA* physician's global assessment, *SDI* Systemic Lupus International Collaborating Clinics/ACR Damage Index, *anti-dsDNA* anti-double stranded DNA, *HCQ* hydroxychloroquine.

* Numbers in bold font indicate statistical significance for $p < 0.05$.

Table 3 Baseline variables associated with LLDAS achievement based on multivariable Cox models

Characteristics	Model 1		Model 2		Model 3	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age at disease onset, years	1.010 (1.003- 1.016)	0.005	1.009 (1.002- 1.016)	0.010	1.010 (1.003- 1.017)	0.004
Treatment-naïve	1.346 (1.105- 1.641)	0.003	1.425 (1.161- 1.749)	0.001	1.484 (1.204- 1.830)	<0.001
Nephritis	0.776 (0.641- 0.939)	0.009	1.066 (0.820- 1.385)	0.634	0.925 (0.737- 1.160)	0.498
SLEDAI			0.968 (0.950- 0.987)	0.001		
PGA					0.685 (0.551- 0.853)	0.001
Daily prednisone (or equivalent) dose, mg/d			1.003 (0.998- 1.007)	0.266	1.005 (0.999- 1.010)	0.093
HCQ	1.638 (1.263- 2.123)	<0.001	1.713 (1.318- 2.225)	<0.001	1.664 (1.284- 2.157)	<0.001

In model 1, the components of LLDAS (daily prednisone dose, SLEDAI and PGA) were not included into the model; In the following models, SLEDAI (model 2) or PGA (model 3) was respectively added into the corresponding model with daily prednisone dose for adjustment. Of note, to avoid the collinearity, SLEDAI and PGA were not included in the same model.

LLDAS Lupus Low Disease Activity State, *HR* hazard ratio, *CI* confidence interval, *SLEDAI-2K* Systemic Lupus Erythematosus Disease Activity Index 2000, *PGA* physician's global assessment, *SDI* Systemic Lupus International Collaborating Clinics/ACR Damage Index, *anti-dsDNA* anti-double stranded DNA, *HCQ* hydroxychloroquine.

Figures

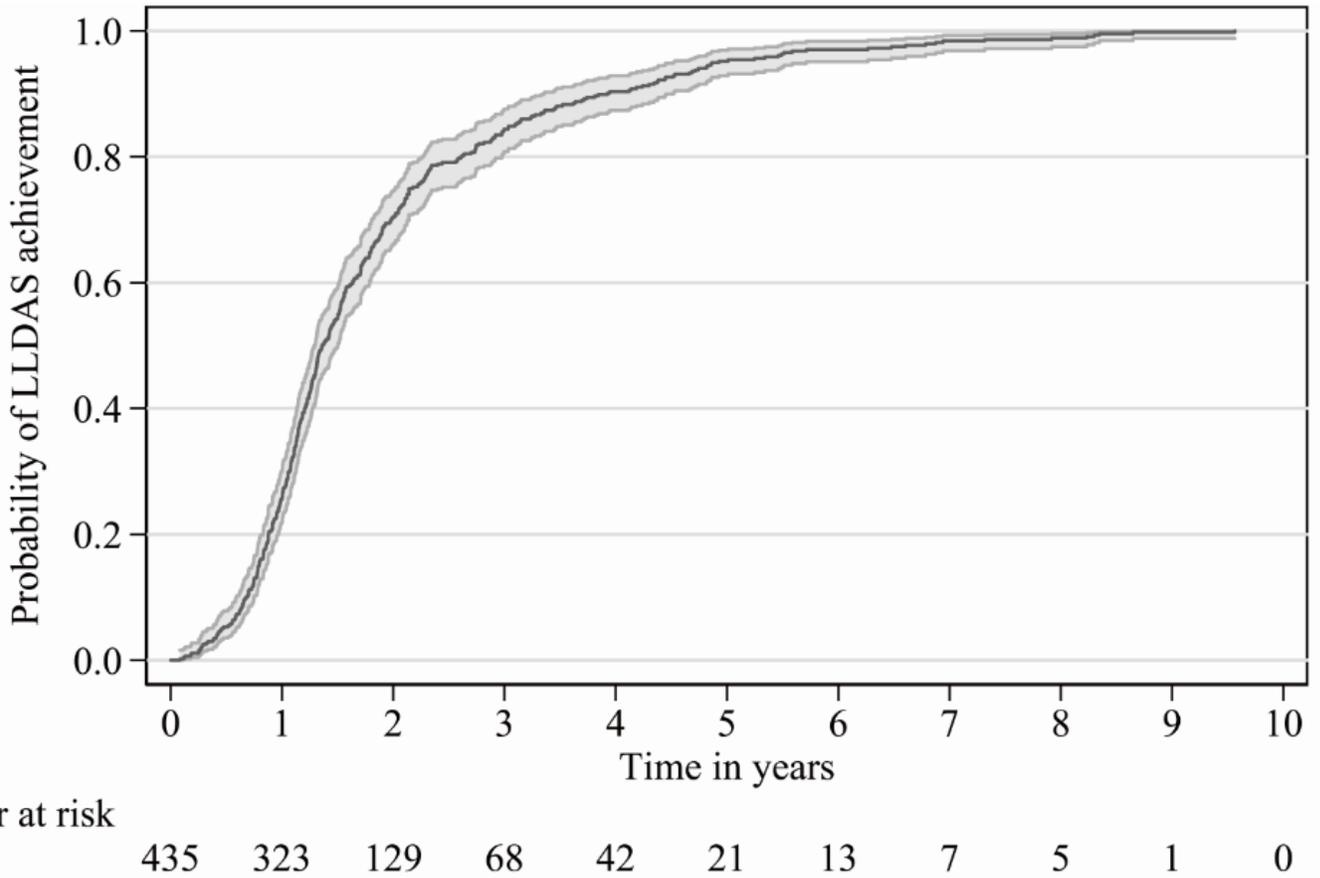


Figure 2

Kaplan-Meier curve for time to Lupus Low Disease Activity State (LLDAS) during 10-year follow-up.

		Time to LLDAS (months)			Age at disease onset
		0-1.0	1.1-2.0	2.1-3.0	
Treatment-naïve	Yes	12.9 (6.6-27.8)	15.9 (13.3-24.1)	20.9 (13.7-41.6)	>30 years
		13.3 (11.0-22.6)	18.0 (13.0-32.9)	23.2 (15.8-35.0)	≤30 years
	No	17.2 (11.7-52.5)	18.5 (12.7-30.9)	32.9 (14.0-82.5)	>30 years
		20.7 (9.4-50.2)	27.5 (16.3-63.0)	54.2 (19.4-114.8)	≤30 years
		PGA			
		0-1.0	1.1-2.0	2.1-3.0	

Figure 4

Matrix model for time to LLDAS. The numbers in each cell of the matrix model represent the median (IQR) time to LLDAS of patients with respective characteristics. SLEDAI-2K was excluded from the matrix model due to the high collinearity with PGA, while HCQ was not included in the matrix model for it was not an objective parameter of patients. Age at disease onset was divided to age at disease onset ≤30

years and age at disease onset >30 years, while PGA was divided to 0-1.0, 1.1-2.0 and 2.1-3.0. Colour scheme: green <18 months, yellow \geq 18 months and <24 months, blue \geq 24 months and <36 months, red \geq 36 months. IQR interquartile range, LLDAS Lupus Low Disease Activity State, PGA physician's global assessment.