

# Predictors of persistent disease activity and long quiescence in systemic lupus erythematosus: results from the Hopkins Lupus Cohort

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## ABSTRACT

**Objectives** The aim of this study is to identify prognostic factors of persistent disease activity and long quiescence in systemic lupus erythematosus (SLE).

**Methods** Patients enrolled in the Hopkins Lupus Cohort from 1987 to 2012, who attended at least three visits per year during 3 consecutive years following baseline and had available information on disease activity were included.

Patterns of SLE disease activity over the 3-year period were defined as: persistent long quiescent (pLQ), persistent relapsing-remitting (pRR), persistent chronic active (pCA) and mixed based on Modified SLE Disease Activity Index (M-SLEDAI). Possible predictors of pCA (vs pLQ, pRR and mixed) and pLQ (vs pCA, pRR and mixed) were identified by univariate and multivariate logistic regression analyses.

**Results** 916 patients were included. In the multivariate analysis, use of hydroxychloroquine (OR: 0.45, 95% CI 0.22 to 0.92,  $p=0.03$ ), African American ethnicity (OR: 2.36, 95% CI 1.15 to 4.85,  $p=0.02$ ) and baseline SLEDAI (OR: 1.10, 95% CI 1.03 to 1.17,  $p=0.005$ ) remained significant predictors of pCA. Higher education (>12 years; OR: 2.07, 95% CI 1.07 to 4.03,  $p=0.03$ ) and lower baseline SLEDAI (OR: 0.67, 95% CI 0.56 to 0.82,  $p<0.001$ ) were significant predictors of pLQ, while African American (OR: 0.38, 95% CI 0.17 to 0.83,  $p=0.02$ ) and female patients (OR: 0.26, 95% CI 0.12 to 0.57,  $p<0.001$ ) were less likely to achieve pLQ.

**Conclusion** African American ethnicity and high disease activity at baseline predict chronic activity in SLE, regardless of treatment, years of education and income. Higher education, low disease activity at baseline and male sex predict long quiescence. The use of hydroxychloroquine is independently associated with a lower risk of chronically active disease.

## INTRODUCTION

The kaleidoscopic nature of systemic lupus erythematosus (SLE) regarding clinical and serological diversity is recognised as a constant challenge in the management of patients with SLE.<sup>1 2</sup> The heterogeneous course of SLE over time is reflected directly in fluctuations of disease activity.<sup>3</sup>

Barr *et al* in 1999 identified three major patterns of disease activity, the chronic active (CA), the relapsing-remitting (RR) and the long quiescent (LQ) by analysing prospectively the disease course of 204 patients in the Hopkins Lupus Cohort based on physician's global assessment (PGA) and the Modified SLE Disease Activity Index (M-SLEDAI). By that time, CA pattern was the most frequent (PGA; 58%, SLEDAI; 40%).<sup>4</sup> Following this study, the definitions of the aforementioned disease activity patterns were applied on accrued data of 28 years from the Hopkins Lupus Cohort identifying the relapsing remitting pattern as the most prevalent pattern (53.8%). The long quiescence pattern (pLQ) and chronic active pattern (pCA) during the first 3 years of disease course were also expressed by patient groups (6.4% and 3.7%, respectively).<sup>5</sup>

It has been shown that chronic disease activity over time<sup>6 7</sup> and especially during the early disease course<sup>8 9</sup> predicts damage accrual in SLE. On the other hand, persistent remission for at least 2 consecutive years based on either SLEDAI-2K or M-SLEDAI, irrespectively of treatment on corticosteroids is protective against damage accrual.<sup>10</sup> Consequently, it is clinically relevant to identify baseline characteristics that predict disease activity and inactivity and thereby to detect modifiable factors that may influence the future disease course.

The aim of this study was to identify prognostic factors of persistent disease activity and long quiescence over 3 years in the Hopkins Lupus Cohort, using baseline demographics and clinical characteristics.

## METHODS

The Hopkins Lupus Cohort is a longitudinal study of patients with SLE enrolled at John

Hopkins University since 1987. According to protocol, patients are followed prospectively every 3 months or at more frequent intervals if there is clinical indication. This analysis was based on the first 3 years of cohort participation among those patients who entered the Hopkins Lupus Cohort prior to or including 2012. Only those patients with three or more visits per year were included. Additionally, adequate information on parameters of disease activity according to SLEDAI for every visit was essential for each patient in order to be included.

Demographical data including age, sex, ethnicity, tobacco use, years of education and combined annual family income were collected and recorded at baseline which was defined as the cohort entry. Education was assessed in years and was applied in analysis categorised as 0–12 years or >12 years. Income was categorised in US dollars into tertiles: <30 000, 30 000–65 000 and ≥65 000. Disease duration was defined as time between diagnosis and inclusion in the cohort. Data on M-SLEDAI, SLEDAI and PGA were prospectively collected at each visit. The M-SLEDAI, modified to remove complement levels and anti-dsDNA antibodies, was used in the present analysis in order to define patterns of disease activity and was scored, based on the presence or absence of disease manifestations, during a month prior to the visit.

Appropriate treatment for SLE was reported at each visit. Immunosuppressive treatment options including azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, chlorambucil as well as biological agents (rituximab, belimumab) were grouped in the analysis under immunosuppressive drug treatment. Hydroxychloroquine and prednisone were applied in the analysis as separate variables. For the evaluation of treatment, each therapeutic option was applied in analyses as dichotomous variable in two different ways: (1) as ever or never received, (2) representing the percentage of visits during which it was received for each patient during the 3 years using 75% of visits as cut-off.

### Definitions of patterns

As previously described in the literature,<sup>4 5</sup> three major patterns of SLE activity have been identified based on the M-SLEDAI when analysing 1-year intervals: long quiescent (LQ), indicating disease that has remained quiescent for at least 1 year (M-SLEDAI=0 at all visits); chronic active (CA), characterised by disease that is constantly active for at least 1 year (M-SLEDAI >0 at each visit) and relapsing remitting (RR), indicating disease where periods of disease activity (M-SLEDAI>0) are interspersed with periods of disease inactivity (M-SLEDAI=0 on one or more visits). Based on the aforementioned definitions, patterns over 3 consecutive years have been defined and applied previously<sup>5</sup> as following: persistent long quiescent (pLQ); LQ pattern is present at each year, persistent relapsing-remitting (pRR); 3 consecutive RR years, persistent chronic active (pCA); 3 consecutive CA years and Mixed, at least two different pattern types (CA, RR or LQ) during a 3-year follow-up interval.

### Statistical analysis

Appropriate parametric statistical tests were used for the analysis of data. All continuous data were examined for normal distribution by Kolmogorov–Smirnov test. Numerical variables with no normal distribution are presented as median values with interquartile range (IQR). Categorical variables are expressed as frequencies. Baseline characteristics and treatment categories were stratified by pattern and by time (decades). Comparison of categorical variables among patterns and time decades was performed using  $\chi^2$  test. Continuous data with a non parametric distribution were analysed and compared among patterns, using the Kruskal/Wallis test.

Possible predictors of pCA (vs pLQ, pRR and mixed) and pLQ (vs pCA, pRR and mixed) at 3-year periods were identified by univariate logistic regression analyses (two separate models). Baseline demographic factors, disease characteristics and treatment categories were used as independent variables in univariate analyses. The results from these analyses ( $p<0.25$  as the criterion) and correlation analyses (Pearson and Spearman correlations) guided the selection of variables for the multivariate logistic regression analyses. For each dependent variable (pLQ or pCA), two separate multivariate models were analysed by applying either treatment as ever/never received or treatment received at ≥/ <75% of follow-up visits. The non-significant variables were removed by stepwise backward selection. Appropriate tests for linearity, interactions and goodness of fit were performed. All statistical analyses were performed with IBM SPSS Statistics V.22.

## RESULTS

### Baseline characteristics

A total 916 patients were included out of 2247 patients. Among the patients who were excluded, 42 patients died during the first 3 years following inclusion in the cohort (36 females, 6 males). All patients met the American College of Rheumatology or Systemic Lupus International Collaborating Clinics classification criteria for SLE.<sup>11 12</sup> A female predominance (91.2%) was observed with median age 37 years. The median disease duration defined as time between diagnosis and cohort inclusion was 2 years. The majority of patients were Caucasians, while a large subgroup belonged to African American ethnicity (38.9%). Disease activity at baseline, based on SLEDAI and PGA, was low (table 1). Baseline characteristics and treatment during 3 years following cohort inclusion were stratified by disease activity pattern (table 2) and calendar time (online supplementary file 1).

### Remission according to DORIS (definitions of remission in SLE)

A further analysis of the pLQ group was conducted by applying the DORIS definitions of remission.<sup>13</sup> A total of 21 patients (35.6%) fulfilled the criteria on remission off therapy (clinical SLEDAI=0, no treatment with prednisone or immunosuppressive drug treatment). Among

**Table 1** Baseline demographic and clinical characteristics

Baseline characteristics	N: 916
Age, years, median (IQR)	37 (19)
Disease duration, years, median (IQR)	2 (7)
SLEDAI, median (IQR)	2 (6)
M-SLEDAI, median (IQR)	0.5 (4)
PGA, median (IQR)	1 (1.5)
Female sex, n (%)	835 (91.2)
Caucasian, n (%)	498 (54.4)
African American, n(%)	356 (38.9)
Higher education, n (%)	565 (61.7)
Smoking, n (%)	138 (15.1)

M-SLEDAI, Modified SLEDAI; PGA, physician's global assessment; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

the 38 patients who had ever received prednisone or immunosuppressive therapy, 10 patients (17% of pLQ group) fulfilled the criteria of remission on therapy

(clinical SLEDAI=0, maintenance dose of immunosuppressive drug treatment and prednisone  $\leq 5$  mg/day).

### Prognostic factors for pLQ pattern

In univariate logistic regression with an outcome pLQ versus all three other patterns, higher education (OR: 2.28, 95% CI 1.21 to 4.28), family income ( $\geq 65$  000; OR: 2.56, 95% CI 1.29 to 5.08) and disease activity at baseline (SLEDAI; OR: 0.62, 95% CI 0.52 to 0.73, PGA; OR: 0.26, 95% CI 0.16 to 0.44) were significant predictors of pLQ pattern. African Americans (OR: 0.23, 95% CI 0.11 to 0.49) and women (OR: 0.34, 95% CI 0.17 to 0.68) were significantly less likely to express pLQ pattern. Patients who had received prednisone during the 3-year period were significantly less likely to be experiencing the pLQ pattern (ever received; OR: 0.53,  $p=0.02$ ,  $\geq 75\%$  of visits; OR: 0.40,  $p=0.002$ ). Patients who had ever received immunosuppressive drug treatment during the 3-year period were less likely to express pLQ pattern (OR: 0.46,  $p=0.007$ ). Smoking at baseline was suggestive (OR: 0.39, 95% CI 0.14 to 1.10,  $p=0.08$ ) (table 3).

Two separate multivariate analyses were processed by applying treatment options as either ever received vs never

**Table 2** Baseline characteristics and treatment during 3-year period stratified by disease activity pattern

	pLQ n: 59	pRR n: 305	pCA n: 34	Mixed n: 518	P values
<b>Baseline characteristics</b>					
Female sex, n(%)	47 (79.7)	285 (93.4)	32 (94.1)	471 (90.9)	0.007
Age, years, median (IQR)	40 (17)	36 (17)	40.5 (27)	37 (20)	0.10
Disease duration, years, median (IQR)	2 (8)	2 (7)	2 (10.3)	2 (6)	0.85
M-SLEDAI at baseline, median (IQR)	0	2 (4)	4 (4)	0 (4)	<0.001
SLEDAI at baseline, median (IQR)	0 (2)	4 (4.5)	4.5 (6.5)	2 (6)	<0.001
PGA at baseline, median (IQR)	0 (0.5)	1 (1)	1 (1.5)	1 (1.5)	<0.001
African American, n(%)	8 (13.6)	132 (43.3)	21 (61.8)	195 (37.6)	<0.001
Caucasian, n(%)	48 (81.4)	151 (49.5)	13 (38.2)	286 (55.2)	<0.001
Education >12 years, n(%)	46 (78)	180 (59.2)	18 (52.9)	321 (62.3)	0.035
Smoking at baseline, n(%)	4 (6.8)	37 (12.1)	9 (26.5)	88 (17)	0.02
<b>Combined family Income \$, n(%)</b>					
<30 000	12 (20.7)	107 (35.9)	17 (50)	159 (31.6)	
30 000–65 000	15 (25.9)	91 (30.5)	7 (20.6)	167 (33.2)	0.05
$\geq 65$ 000	31 (53.4)	100 (33.5)	10 (29.4)	177 (35.2)	
<b>Treatment during 3 years</b>					
<b>Prednisone, n(%)</b>					
Ever received	36 (61)	243 (79.7)	23 (67.6)	375 (72.4)	0.009
$\geq 75\%$ of visits	18 (30.5)	182 (59.7)	18 (52.9)	249 (48.1)	<0.001
<b>Hydroxychloroquine, n (%)</b>					
Ever received	43 (72.9)	243 (79.7)	20 (58.8)	397 (76.7)	0.04
$\geq 75\%$ of visits	40 (67.8)	184 (60.3)	15 (44.1)	309 (59.7)	0.17
<b>Immunosuppressive drug treatment, n (%)</b>					
Ever received	19 (32.2)	165 (54.1)	14 (41.2)	257 (49.6)	0.01
$\geq 75\%$ of visits	14 (23.7)	89 (29.2)	10 (29.4)	143 (27.6)	0.85

M-SLEDAI, Modified SLEDAI; PGA, physician's global assessment; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

**Table 3** Predictors of pLQ; univariate analysis

Univariate analysis pLQ vs other*	P values	OR	95% CI
Female sex	0.002	0.34	0.17 to 0.68
Age >40 years	0.51	1.19	0.70 to 2.03
Disease duration†	0.57	1.01	0.97 to 1.05
African American	<0.001	0.23	0.11 to 0.49
Years of education >12 years	0.01	2.28	1.21 to 4.28
Income \$			
<30 000		ref	
30 000–65 000	0.47	1.34	0.61 to 2.90
≥65 000	0.007	2.56	1.29 to 5.08
Smoking at baseline	0.08	0.39	0.14 to 1.10
SLEDAI baseline†	<0.001	0.62	0.52 to 0.73
PGA baseline†	<0.001	0.26	0.16 to 0.44
Immunosuppressive drug treatment			
1. Ever received	0.007	0.46	0.26 to 0.81
2. ≥75% of visits	0.46	0.79	0.43 to 1.47
Hydroxychloroquine			
1. Ever received	0.47	0.80	0.44 to 1.46
2. ≥75% of visits	0.20	1.45	0.82 to 2.54
Prednisone			
1. Ever received	0.02	0.53	0.31 to 0.91
2. ≥75% of visits	0.002	0.40	0.23 to 0.71

\*pLQ: n:59, other: pCA, pRR and mixed: n:857.

†per unit.

pCA, persistent chronic active; PGA, physician's global assessment; pLQ, persistent long quiescent; pRR, persistent relapsing remitting; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

received or received at ≥75% of visits vs <75% of visits. No treatment option remained in any multivariate analysis, thereby the final model was the same in both analyses. Higher education (OR: 2.07, 95% CI 1.07 to 4.03) and SLEDAI score at baseline (OR: 0.67, 95% CI 0.56 to 0.82) remained significant independent predictors of pLQ pattern. Female patients (OR: 0.26, 95% CI 0.12 to 0.57) and African American patients (OR: 0.38, 95% CI 0.17 to 0.83) were significantly less likely to express long quiescence over 3 years (table 4).

**Table 4** Predictors of pLQ; multivariate analysis

Multivariate analysis pLQ vs other*	P values	OR	95% CI
Female sex	0.001	0.26	0.12 to 0.57
African American	0.02	0.38	0.17 to 0.83
SLEDAI baseline†	<0.001	0.67	0.56 to 0.82
Education >12 years	0.03	2.07	1.07 to 4.03

\*pLQ: n:59, other: pCA, pRR and mixed: n:857.

†per unit.

pCA, persistent chronic active; pLQ, persistent long quiescent; pRR, persistent relapsing remitting; SLE, systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

**Table 5** Predictors of pCA; univariate analysis

Univariate analysis pCA vs other*	P values	OR	95% CI
Female sex	0.54	1.57	0.37 to 6.69
Age >40 years	0.32	1.42	0.71 to 2.81
Disease duration†	0.17	1.03	0.99 to 1.08
African American	0.007	2.64	1.30 to 5.34
Years of education >12 years	0.27	0.68	0.34 to 1.35
Income \$			
<30 000		ref	
30 000–65 000	0.06	0.42	0.17 to 1.03
≥65 000	0.12	0.53	0.24 to 1.18
Smoking at baseline	0.06	2.10	0.96 to 4.60
SLEDAI baseline†	0.002	1.10	1.04 to 1.17
PGA baseline†	0.04	1.51	1.03 to 2.23
Immunosuppressive drug treatment			
1. Ever received	0.32	0.70	0.35 to 1.40
2. ≥75% of visits	0.85	1.08	0.51 to 2.29
Hydroxychloroquine			
1. Ever received	0.01	0.42	0.21 to 0.84
2. ≥75% of visits	0.06	0.52	0.26 to 1.03
Prednisone			
1. Ever received	0.40	0.73	0.35 to 1.52
2. ≥75% of visits	0.82	1.09	0.55 to 2.16

\*pCA: n:34, other: pLQ, pRR and mixed: n:882

†per unit.

pCA, persistent chronic active pattern; PGA, physician's global assessment; pLQ, persistent long quiescent; pRR, persistent relapsing remitting; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

### Prognostic factors for pCA pattern

In univariate analysis, African American ethnicity (OR: 2.64, 95% CI 1.30 to 5.34) and disease activity at baseline were significant prognostic factors for pCA pattern (SLEDAI; OR: 1.10, 95% CI 1.04 to 1.17, PGA; OR: 1.51, 95% CI 1.03 to 2.23). Patients who received hydroxychloroquine at ≥75% of follow-up were borderline less likely to be experiencing the pCA pattern according to univariate analysis (OR: 0.52, 95% CI 0.26 to 1.03, p=0.06). When hydroxychloroquine was applied in the univariate analysis as ever versus never received this relationship was shown to be significant (OR: 0.42, 95% CI 0.21 to 0.84, p=0.01). Smoking and family income at baseline showed both a strong tendency towards statistical significance (p=0.06) (table 5).

In the multivariate model by applying treatment as ever vs never received, the use of hydroxychloroquine was significantly associated with a lower risk of expressing pCA (OR: 0.45, 95% CI 0.22 to 0.92). African American ethnicity (OR: 2.36, 95% CI 1.15 to 4.85) and SLEDAI score (OR: 1.10, 95% CI 1.03 to 1.17) remained independent predictive factors for pCA. In multivariate analysis applying treatment as received ≥75% vs <75% of follow-up,

**Table 6** Predictors of pCA; multivariate analysis (two separate final models)

Multivariate analysis pCA vs other*	P values	OR	95% CI
<b>First model (treatment ever vs never received)</b>			
African American	0.02	2.36	1.15 to 4.85
SLEDAI baseline†	0.005	1.10	1.03 to 1.17
Hydroxychloroquine	0.03	0.45	0.22 to 0.92
<b>Second model (treatment received <math>\geq 75\%</math> of visits vs other)</b>			
African American	0.01	2.43	1.19 to 4.94
SLEDAI baseline†	0.004	1.09	1.03 to 1.16

\*pCA: n:34, other: pLQ, pRR and mixed: n:882.

†per unit.

pCA, persistent chronic active pattern; PGA, physician's global assessment; pLQ, persistent long quiescent; pRR, persistent relapsing remitting; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

African American ethnicity and SLEDAI score remained independent predictive factors for pCA (table 6).

## DISCUSSION

This study identified prognostic factors of persistent activity and long quiescence in the Hopkins Lupus Cohort. This is the first study to predict persistent patterns of disease activity based on assessment of M-SLEDAI on at least three time points per year. Clinically relevant information regarding the role of treatment, ethnicity, education and disease activity at baseline on the development of discrete disease activity patterns is derived from the analysis.

The most striking finding of this study is that the use of hydroxychloroquine ever during early disease course is significantly and independently associated with a lower risk of expressing persistent activity early in the course of SLE. This association approached statistical significance ( $p=0.06$ ) even when hydroxychloroquine was applied in the univariate analysis as a treatment option received on the longer part of the aforementioned time period ( $\geq 75\%$  of visits in three consecutive years following baseline). It is undoubtedly difficult to evaluate the role of treatment on disease activity patterns because of reverse causality; disease course influences treatment decisions and vice versa. Persistent activity may lead to more aggressive therapy, and, likewise, lack of disease activity may result in cutting down treatment. This can explain the significantly lower percentage of pLQ patients receiving prednisone ( $\geq 75\%$  of visits; 30.5%,  $p<0.001$ ). This is not the case, however, with hydroxychloroquine, as it is regarded as a basic therapeutic factor in SLE and is recommended to patients with SLE irrespectively of disease activity.<sup>14–17</sup> The role of hydroxychloroquine as an immunomodulator with benefits in specific disease manifestations such as cutaneous disease, nephritis and thrombosis but also in the prevention of SLE and reduction of flares has been confirmed in a number of studies and recently reviewed.<sup>18</sup>

Our data confirm that hydroxychloroquine contributes to a favourable disease course in an early stage by reducing persistent activity measured by a validate disease instrument.

One of the most consistent results in this study is that, compared with other ethnicities, African Americans are significantly prone to a chronic disease activity pattern independently of socioeconomic factors. Despite the fact that the effect of socioeconomic status on explaining ethnic differences in SLE has been under discussion,<sup>19</sup> there are a number of studies which agree with this finding. In LUMINA cohort, consisting of a large multiethnic population (554 patients), African-American ethnicity predicted high levels of disease activity based on SLAM-R score over the course of the disease independently of socioeconomic status.<sup>20</sup> In the SLICC inception cohort, African American patients had higher SLEDAI score than Caucasians over the first 5 years of disease course, though it did not reach statistical significance.<sup>21</sup> A recent study in Hopkins Lupus Cohort analysed the time needed to achieve remission in patients that were not in remission at baseline according to DORIS definitions and showed that African American ethnicity was significantly associated with a longer time to remission.<sup>22</sup> It has been implicated that genetic factors influence the expression of SLE in an early stage while non-genetic factors modify the overall disease course and thus determine the prognosis and survival of patients with SLE.<sup>23 24</sup> Such a notion is supported by studies in the Hopkins Lupus Cohort. In a previous study in the same cohort, Kasitanon *et al* have found that African Americans had poorer survival compared with other ethnicities, influenced partly by income when applied in the multivariate analysis.<sup>9</sup> Ethnicity as a concept consists of genetic, cultural and social aspects and thus ethnic groups cannot be considered as genetically homogeneous groups.<sup>25</sup> Nonetheless, our multivariate analysis, controlling for socioeconomic factors such as annual family income and education as possible confounders, suggests that African American ethnicity presents intrinsic susceptibility to a chronically active SLE course.

Higher education was also found in the current analysis to be an independent predictor of persistent inactivity. Consistent with our findings, a multicentre study in Canada which included African American in a smaller percentage (7.7%) showed that low education (less than 12 years) was associated with higher SLEDAI score at baseline, even after adjustment for age, ethnicity and gender.<sup>26</sup> A possible explanation to the association of higher education and pLQ pattern is that higher education is associated with stronger adherence to treatment decisions leading to favourable disease outcomes such as disease inactivity. The effect of educational status on drug adherence has been implied by studies conducted on cutaneous lupus and cardiovascular diseases.<sup>27 28</sup> Additionally, it has been shown that education prompts a healthy behaviour pattern by affecting cognitive ability.<sup>29</sup>

Regarding gender and its prognostic role on disease activity patterns, this study has showed that male patients were significantly more likely to express long quiescence during the 3-year analysed period. This finding may be considered as paradoxical as it comes in contrast with literature according to which male gender is associated with increased damage accrual<sup>7 30</sup> and lower survival.<sup>31</sup> It has been shown earlier in the Hopkins Lupus Cohort that male patients had significantly shorter 20-year survival than females (68% vs 79%)<sup>9</sup>. Given the interaction of disease activity-damage accrual-survival, males in our study should have been prone to persistent disease activity. A possible explanation could be that a considerable percentage of male patients died shortly after inclusion in the cohort due to severe disease course without being included in the study. In that way, male patients with persistent activity could be under-represented in the study. However, we have rejected this assumption as the percentage of male patients who died shortly after inclusion in the cohort and thereby excluded from the study does not differ significantly from the percentage of men in the study population (8.8% vs 14.3%, respectively,  $p=0.26$ ). It is worth to mention that there are studies which suggest no difference regarding disease activity between males and females. Andrade *et al* have shown that despite the increased damage accrual in men with SLE compared with women, disease activity based on SLAM-R was comparable.<sup>30</sup> In a large Latin-American cohort, the maximum SLEDAI score between males and females did not differ statistically.<sup>32</sup>

Higher disease activity at baseline based on M-SLEDAI was found to be an independent predictor of pCA pattern and likewise lower disease activity at baseline predicted pLQ pattern. This result confirms previous findings regarding the predictive value of the assessment of disease activity early in the disease course on the overall disease activity.<sup>8 20</sup>

The current study was conducted in one of the largest SLE cohorts, following up patients prospectively up to 28 years. Additionally to its large population size and the long follow-up, the Hopkins Lupus Cohort provides an ideal research design based on which patients are followed quarterly by protocol or more often if there is a clinical indication. In that way, real time disease course was captured in this study, based on both study and clinical visits. Moreover, the current study, by enabling patients with low disease activity over an early period of follow-up to be included in the analysis, evaluated a population that is under-represented, since most studies demand a level of activity in inclusion criteria.

There are several limitations in this study that have to be addressed. The high percentage of African American patients in the study population in contrast to other cohorts may weaken the generalisability of our findings in other cohorts. Due to strict definitions of disease activity patterns, the size of pLQ and pCA groups is small. It is possible that we have underestimated pLQ group by excluding cases of low disease activity which did not fulfil

the definitions. Considering the possibility that patients on remission may have skipped follow-up, pLQ may have been additionally underestimated. We also acknowledge that the level of disease activity for each patient at the time of inclusion in the cohort was a determinant of the disease activity pattern during the 3-year period. In that way, patients who entered the cohort with active disease did by definition not enter the pLQ group; if they manage to show disease inactivity during the first 3 years, they would enter the relapsing remitting or mixed group. Along with the fact that disease activity patterns in our study were defined more than a decade before DORIS criteria of remission, we cannot claim that we analysed the possibility of remission throughout the disease course. However, we conducted a further analysis in the pLQ group by applying DORIS definitions of remission in this population; more than half of the pLQ group fulfilled the criteria of remission either on or off therapy. Moreover, we acknowledge that we evaluated an early period in the disease course of each patient but we did not capture the period directly following the onset of SLE in the majority of patients (median disease duration: 2 years). In that way, we have not analysed disease activity at the point where patients were naïve to treatment. Important to be mentioned is, however, that median disease duration did not differ among patterns. Thus, the development of discrete disease activity patterns cannot be attributed to different disease duration.

Overall, this study provides insight into the outline of disease course over an early stage by identifying ethnicity, education, disease activity at baseline and treatment as determinants of specific disease activity patterns. Additional action is prompted, early in the course of SLE, in the management of African American patients as well as patients with high SLEDAI score as they are prone to persistent disease activity. This analysis supports the use of hydroxychloroquine early in the course of the disease and abstention from smoking in order to increase the likelihood of disease inactivity in SLE.

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