

# Predictors of Organ Damage Progression and Effect on Health-related Quality of Life in Systemic Lupus Erythematosus

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**ABSTRACT. Objective.** To describe organ damage accrual, predictors of damage progression, and effect on health-related quality of life (HRQOL) in patients with systemic lupus erythematosus (SLE).

**Methods.** A longitudinal database of patients who met the American College of Rheumatology (ACR) classification criteria for SLE was used. Annual assessments included the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) and the Medical Outcomes Study Short Form-36 (SF-36). The prognostic significance of demographic, disease-related, and treatment-related factors on damage progression was examined using multivariable Cox regression. The effect of changes in SDI scores on HRQOL, measured using the SF-36 summary and subscale scores, was assessed using linear mixed-effects modeling.

**Results.** There were 273 patients with SLE studied over a mean (SD) duration of followup of 7.3 (4.3) years. During followup, 126 (46.2%) had an increase in SDI scores. Patients with preexisting damage at baseline were more likely to have earlier damage progression (HR 2.09, 95% CI 1.44–3.01). Older age,  $\geq 8$  ACR classification criteria, immunosuppressive drugs, cigarette smoking, and higher mean serum C-reactive protein levels were associated with an earlier increase in SDI scores in multivariable analysis. In general, changes in SDI scores were associated with initial declines in SF-36 scores at the time that damage occurred, with subsequent change comparable to that seen in patients without damage progression.

**Conclusion.** This study identified multiple risk factors, some modifiable, associated with damage progression in patients with SLE. The negative effect on HRQOL emphasizes the need for treatment strategies to reduce the risk of organ damage over time. (J Rheumatol First Release April 15 2016; doi:10.3899/jrheum.150985)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS DAMAGE HEALTH-RELATED QUALITY OF LIFE

Systemic lupus erythematosus (SLE) is a complex multi-system autoimmune disease with the potential to affect every organ system in the body. The clinical course of SLE is highly variable, ranging from a relatively benign illness to gradually progressive organ damage, fulminant organ failure, and death. Given the variability of health trajectories among patients with SLE, it is crucial to be able to identify those patients at highest risk for adverse outcomes.

Organ damage, assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI), has been

identified as an important factor in determining the risk of adverse longterm outcomes in SLE. The SDI has been shown to be predictive of future mortality, such that patients with higher damage scores are at increased risk of premature death<sup>1,2,3,4</sup>. Therefore, it is essential to understand the factors associated with the development of organ damage in patients with SLE, to identify patients at highest risk for damage accrual, and to target interventions to reduce the progression of damage over time.

Outcome studies assess patients with SLE across 3 disease dimensions: global disease activity, cumulative organ damage, and health-related quality of life (HRQOL)<sup>5</sup>. The availability of validated instruments for the measurement of these outcomes facilitates further investigation of their interactions. In particular, the relationship between cumulative organ damage and HRQOL in SLE remains poorly understood.

We used longitudinal assessments in an SLE cohort to describe how cumulative organ damage develops and progresses over time. In addition, we evaluated the effect of key disease-related factors, medical therapies, demographic variables, and serological biomarkers on the rate of damage accrual to identify predictors of damage progression. We also

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Accepted for publication February 25, 2016.

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examined the relationship between cumulative organ damage and HRQOL. We hypothesized that as damage progresses over time in patients with SLE, HRQOL would be impaired, such that patients who exhibit more damage accrual would also demonstrate lower HRQOL.

## MATERIALS AND METHODS

**Patients.** Consecutive patients enrolled in the Dalhousie Lupus Clinic Registry from 2000–2014 at the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada, were considered for our study. The clinic receives referrals from primary care physicians, general internists, rheumatologists, and other subspecialists in a referral base of about 1 million people. It is the only designated SLE clinic in the Atlantic Canada region.

The registry is a comprehensive longitudinal database of patients with SLE who have been followed in the clinic for up to 14 years. All patients fulfilled the ACR criteria for SLE<sup>6</sup>, which was taken as the date of diagnosis of SLE. Patients were evaluated upon enrollment and each year thereafter using standardized annual assessments. Those who had at least 2 registry visits where cumulative organ damage had been assessed were selected for our current study. The study protocol was approved by the Capital Health (now Nova Scotia Health Authority) Research Ethics Board.

**Study assessments.** Data acquisition included a medical history and physical examination, review of the patient's medical record, and completion of standardized instruments for the quantification of disease activity, cumulative organ damage, and HRQOL. Peripheral blood was collected at baseline and at each subsequent visit for the evaluation of hematological, biochemical, and serologic variables relevant to the assessment of SLE.

Demographic features at the baseline visit included age, sex, disease duration, and level of education attained. The ACR classification criteria met at baseline were also recorded. Global SLE disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)<sup>7</sup>.

Cumulative organ damage was measured using the SDI. The SDI contains items that represent irreversible organ damage (ordinarily present for at least 6 mos) occurring after the diagnosis of SLE, regardless of attribution<sup>8</sup>. Because the items in the SDI are permanent, the SDI score cannot decrease over time. In our study, damage progression was assessed using time to first change in SDI score.

HRQOL was measured using the Medical Outcomes Study Short Form-36 (SF-36), an extensively validated and commonly used instrument to evaluate HRQOL in patients with SLE<sup>9</sup>.

SLE-related medications were documented, in particular corticosteroids, antimalarials, and immunosuppressive drugs (methotrexate, azathioprine, cyclophosphamide, leflunomide, or mycophenolate mofetil). Biologic agents were not included in the analysis because their use was minimal. Medication use variables were defined as any use of a medication from a given class at any timepoint from the baseline study visit up to the time of first change in SDI. Duration of use, as well as use of multiple agents from the same class, were not considered. The dose of corticosteroids at each clinic visit was recorded. Lifestyle habits and comorbidities included cigarette smoking, diabetes mellitus (identified from the SDI or use of diabetic medications), and hypertension (HTN; systolic blood pressure > 140 and/or diastolic blood pressure > 90 and/or use of antihypertensive medication). Laboratory variables included antiphospholipid antibodies (aPL; IgG anticardiolipin or lupus anticoagulant) and inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)].

**Statistical analysis.** Baseline characteristics are presented as means with SD for continuous variables and frequencies with percentages for categorical data. Using multivariable Cox proportional-hazards models, the prognostic significance of factors known or perceived to be associated with disease progression was examined. These variables included age, sex, disease duration, total number of and individual ACR classification criteria for SLE met at baseline, mean SLEDAI-2K score up to time of first change in SDI,

any use of corticosteroids, antimalarials, or immunosuppressive medications up to time of first change in SDI, presence of aPL at baseline, mean ESR and CRP levels up to time of first SDI change, presence of comorbid HTN or diabetes, cigarette smoking, and level of education attained. The final model included any factor found to be possibly associated on univariable analysis ( $p < 0.05$ ). The proportionality assumption was not violated in any of the models considered. Parallel curves resulted in the analysis of the survival function versus time and the log (–log survival) versus log of the survival time.

To evaluate the longitudinal relationship between organ damage progression and HRQOL, the effect of changes in SDI scores on SF-36 subscales and summary scores was assessed. Linear mixed-effects modeling was used for repeated measures over time to control for within subject correlation. HRQOL was the dependent variable, and effects for time, change in SDI from baseline, and time by SDI change interaction were examined using an unstructured covariance matrix. Where interaction was not found at an  $\alpha$  level of significance  $< 0.10$ , model results are presented using time and SDI change as independent predictors only. All other statistical comparisons were 2-sided using a significance level of  $p = 0.05$ . Analyses were conducted in SAS version 9.4.

## RESULTS

**Patients.** A total of 273 patients with SLE were studied (Table 1). They were predominantly women (87.2%) and white (92%) with a mean (SD) age of 44.1 (14.6) years. At enrollment, the mean (SD) disease duration was 7.5 (8.6) years. There were 112 patients (41.0%) in the cohort who were enrolled within 12 months of SLE diagnosis. The spectrum of ACR criteria was in keeping with other SLE cohorts<sup>10</sup>. One hundred ninety-six patients (71.8%) had no prior organ damage at baseline (SDI = 0), while the remaining 77 patients (28.2%) had preexisting damage (baseline SDI  $\geq 1$ ). Twenty-seven patients (9.9%) died during followup, while 37 additional patients (13.6%) were lost to followup.

**Cumulative organ damage over time.** The mean (SD) duration of followup was 7.3 (4.3) years. There were 147 patients (53.8%) with SLE who had no increase in SDI score during followup, indicating no change in cumulative organ damage. The remaining 126 patients (46.2%) had an increase of  $\geq 1$  in SDI score. The distribution of change in SDI scores from baseline for patients in the cohort is shown in Table 2.

**Predictors of damage.** The factors associated with earlier time to first change in SDI on univariable analysis are summarized in Table 3. Variables associated with an increase in SDI scores included older age at baseline (HR 1.03, 95% CI 1.02–1.05), longer disease duration (1.03, 1.01–1.05), current or past cigarette smoking (2.07, 1.37–2.98), preexisting organ damage at baseline (baseline SDI  $\geq 1$ ; 2.09, 1.44–3.01), immunosuppressive medication use at any time up to first change in SDI (1.80, 1.23–2.63),  $\geq 8$  ACR criteria at baseline (2.39, 1.24–4.63), presence of serositis at baseline (1.47, 1.01–2.15), and mean ESR (per unit; 1.01, 1.00–1.02) and CRP (per unit; 1.01, 1.00–1.02) levels up to the time to first change in SDI. Patients with SLE who had completed college at baseline were found to be less likely to have early damage progression when compared with patients with lower levels of educational attainment (0.56, 0.35–0.92).

Table 1. Demographic and clinical manifestations of patients with SLE at enrollment. Values are n (%) unless otherwise specified.

Characteristics	Values
No. patients	273
Duration of followup, yrs, mean (SD)	7.3 (4.3)
Age, yrs, mean (SD)	44.1 (14.6)
Sex	
Male	35 (12.8)
Female	238 (87.2)
Disease duration, yrs, mean (SD)	7.5 (8.6)
No. ACR criteria at baseline	
4	99 (36.3)
5	76 (27.8)
6	55 (20.2)
7	26 (9.5)
8+	17 (6.2)
ACR classification criteria	
Serositis	81 (29.7)
Mucocutaneous	207 (75.8)
Arthritis	190 (69.6)
Renal disease	71 (26.0)
Neurological disorder	16 (5.9)
Hematological disorder	190 (69.6)
Immunological disorder	231 (84.6)
ANA-positive	272 (99.6)
aPL	76 (27.8)
Medications	
Corticosteroids	156 (57.1)
Antimalarials	209 (76.6)
Immunosuppressives	109 (39.9)
SLEDAI-2K score, mean (SD)	3.1 (4.3)
Baseline SDI score	
0	196 (71.8)
≥ 1	77 (28.2)
Smoking, current/past	143 (52.4)
Hypertension	36 (13.2)
Diabetes	14 (5.1)

SLE: systemic lupus erythematosus; ACR: American College of Rheumatology; ANA: antinuclear antibody; aPL: antiphospholipid antibodies; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index.

Table 2. Distribution of change in SDI scores from baseline during followup. Values are n (%).

Change in SDI Scores from Baseline	No. Patients
0	147 (53.8)
1	57 (20.9)
2	37 (13.5)
3	18 (6.6)
4	6 (2.2)
5	3 (1.1)
6	3 (1.1)
7	1 (0.4)
11	1 (0.4)

SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Variables not significantly associated with an earlier increase in SDI scores were patient sex, SLEDAI-2K score up to time of first change in SDI, corticosteroid or antimalarial use up to time to first SDI change, presence of aPL at baseline, or presence of comorbidities including HTN and diabetes.

Variables found to be statistically significant in univariable analyses were then included in a multivariable analysis of factors associated with time to first increase in SDI scores (Table 3). Given the collinearity between the inflammatory markers ESR and CRP, only 1 of these variables, CRP, was included in multivariable analysis. Older age at baseline (HR 1.03, 95% CI 1.01–1.05), ≥ 8 ACR criteria at baseline (2.29, 1.09–4.82), immunosuppressive medication use up to time to first SDI change (1.82, 1.21–2.73), mean serum CRP level up to time of first SDI change (1.01, 1.00–1.02), and current or past cigarette smoking (1.69, 1.10–2.60) remained statistically significant in multivariable analysis.

*Damage and HRQOL.* Table 4 summarizes the change in the SF-36 subscales, physical component summary (PCS) scores and mental component summary (MCS) scores, over time and the effect of the changes in SDI scores on SF-36 scores. The Visit Number variable in Table 4 describes how SF-36 scores changed with each clinic visit, independent of patient age at baseline and changes in the SDI. None of the Visit Number estimates were statistically significant, suggesting that SF-36 scores did not change significantly as duration of followup increased.

The Age variable shows the effect of baseline patient age on SF-36 scores. Physical Function, Physical Role, and Body Pain subscale scores, as well as the PCS score, were lower among older patients and these results reached statistical significance. Older age at baseline was also associated with lower scores in the General Health subscale, although this result was of borderline statistical significance ( $p = 0.050$ ). In contrast to these results, older patients with SLE were actually more likely to have higher MCS scores ( $p = 0.015$ ).

The Change SDI variable describes the change in SF-36 scores at the time of an increase in SDI score by 1 unit, thus describing the effect of a change in cumulative organ damage on HRQOL at the time of the change. For PCS and MCS scores as well as for all subscale scores, a change in SDI was associated with an initial decrease in SF-36 scores at the time that the SDI change was documented. This relationship was statistically significant for all scores, with the exception of the MCS score ( $p = 0.079$ ) and the Social Function ( $p = 0.059$ ) and Body Pain ( $p = 0.063$ ) subscales, where there was borderline statistical significance.

The interaction term “Change SDI × Visit Number” evaluated the effect of a change in SDI score on the rate of change in SF-36 scores over time. The interaction term was not statistically significant for any score with the exception of the General Health subscale. Nonsignificant interactions suggested that for each increase in SDI score, there was a

Table 3. Univariable and multivariable analyses of predictors for earlier time to first change in SDI score.

Characteristics	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Older age	1.03 (1.02–1.05)	<b>&lt; 0.001</b>	1.03 (1.01–1.05)	<b>&lt; 0.001</b>
Female	0.86 (0.50–1.46)	0.57		
Disease duration, per day	1.03 (1.01–1.05)	<b>0.01</b>	1.00 (0.98–1.02)	0.90
Baseline SDI				
0 at baseline	Reference			
1+ at baseline	2.09 (1.44–3.01)	<b>&lt; 0.001</b>	1.42 (0.93–2.19)	0.11
No. ACR criteria				
< 8 at baseline	Reference			
≥ 8 at baseline	2.39 (1.24–4.63)	<b>0.01</b>	2.29 (1.09–4.82)	<b>0.03</b>
Mean SLEDAI-2K score	1.05 (0.97–1.14)	0.22		
Corticosteroid use	1.36 (0.89–2.07)	0.16		
Average visit dose of steroids	0.99 (0.97–1.01)	0.50		
Antimalarial use	0.96 (0.55–1.65)	0.87		
Immunosuppressive use	1.80 (1.23–2.63)	<b>0.002</b>	1.82 (1.21–2.73)	<b>0.004</b>
Presence of aPL at baseline	0.95 (0.65–1.41)	0.81		
Mean ESR up to first change in SDI	1.01 (1.00–1.02)	<b>0.001</b>		
Mean CRP up to first change in SDI	1.01 (1.00–1.02)	<b>&lt; 0.001</b>	1.01 (1.00–1.02)	<b>0.002</b>
Hypertension	1.41 (0.82–2.41)	0.21		
Diabetes	1.51 (0.70–3.24)	0.29		
Smoking status				
Never	Reference			
Past or current	2.07 (1.37–2.98)	<b>&lt; 0.001</b>	1.69 (1.1–2.6)	<b>0.02</b>
Education				
Did not complete high school	Reference			
Completed high school	0.80 (0.51–1.25)	0.32	1.21 (0.74–1.97)	0.44
Completed college	0.56 (0.35–0.92)	<b>0.02</b>	0.98 (0.56–1.71)	0.94
ACR criteria				
Serositis	1.47 (1.01–2.15)	<b>0.045</b>	0.83 (0.53–1.28)	0.40
Mucocutaneous manifestations	1.28 (0.82–2.00)	0.28		
Arthritis	0.89 (0.60–1.33)	0.58		
Renal manifestations	0.87 (0.57–1.32)	0.51		
Neurological manifestations	1.21 (0.56–2.60)	0.63		
Hematological manifestations	1.10 (0.75–1.62)	0.63		
Immunological manifestations	1.06 (0.64–1.78)	0.81		

Significant data are in bold face. ACR: American College of Rheumatology; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; aPL: antiphospholipid antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

prompt fall in PCS and MCS scores and in the majority of SF-36 subscale scores; however, any subsequent decline was the same age-related change that occurred in all patients. Thus, following the drop in SF-36 scores related to a change in SDI, the scores did not appear to recover and did not continue to decline above the “normal” age-related rate.

For the General Health subscale, the interaction term was statistically significant with a positive variable estimate. This indicated that after the initial drop in General Health scores following an increase in SDI scores, the slope of the curve changed in the positive direction, suggesting that there was a slight recovery in the General Health scores following the initial decline, although scores did not recover completely (Figure 1).

## DISCUSSION

In this single-center cohort of patients with SLE followed

longitudinally for up to 14 years, 46.2% of patients developed at least 1 damage item during followup. Our study confirms the findings of others that patients with SLE with preexisting damage at baseline are more likely to develop further damage over time<sup>1,2,11,12</sup>. We have also identified other risk factors for earlier damage accrual, including older age at study baseline, greater number of ACR classification criteria at baseline, immunosuppressive use up to first SDI change, current or past cigarette smoking, and higher mean ESR and CRP levels up to time to first damage progression. Finally, we examined the complex relationship between change in organ damage and HRQOL over time.

Because patients with SLE with higher damage scores have increased mortality<sup>1,2,3,4</sup>, it is important to understand the factors associated with the development of organ damage over time. In our current study, univariable analysis indicated that both older age and longer disease duration were

Table 4. Effect of changes in SDI scores on HRQOL as measured by the SF-36 subscales and summary scores. Variable estimates signify the change in SF-36 scores per 1 unit change in visit number, baseline age, or SDI score. Values are model variables estimates (SE), p value.

Variables	Visit Number	Age	Change SDI	Change SDI × Visit Number Interaction Term
PCS	-0.12 (0.1), p = 0.25	-0.28 (0), <b>p &lt; 0.001</b>	-0.72 (0.3), <b>p = 0.036</b>	
MCS	0.16 (0.1), p = 0.11	0.11 (0), <b>p = 0.015</b>	-0.64 (0.4), p = 0.079	
General health	0.18 (0.2), p = 0.32	-0.18 (0.1), p = 0.050	-3.92 (0.9), <b>p &lt; 0.001</b>	0.26 (0.1), <b>p = 0.008</b>
Body pain	-0.25 (0.2), p = 0.24	-0.23 (0.1), <b>p = 0.007</b>	-1.38 (0.7), p = 0.063	
Mental health	0.17 (0.1), p = 0.25	0.05 (0.1), p = 0.48	-1.19 (0.5), <b>p = 0.026</b>	
Physical function	-0.16 (0.2), p = 0.47	-0.65 (0.1), <b>p &lt; 0.001</b>	-1.55 (0.7), <b>p = 0.024</b>	
Emotional role	0.55 (0.3), p = 0.07	0.04 (0.1), p = 0.75	-2.39 (1.2), <b>p = 0.038</b>	
Physical role	-0.11 (0.4), p = 0.75	-0.62 (0.1), <b>p &lt; 0.001</b>	-2.99 (1.3), <b>p = 0.021</b>	
Social function	0 (0.2), p = 0.999	-0.07 (0.1), p = 0.43	-1.49 (0.8), p = 0.059	
Vitality	0.01 (0.2), p = 0.95	-0.14 (0.1), p = 0.101	-1.38 (0.7), <b>p = 0.040</b>	

Significant data are in bold face. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; HRQOL: health-related quality of life; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary.

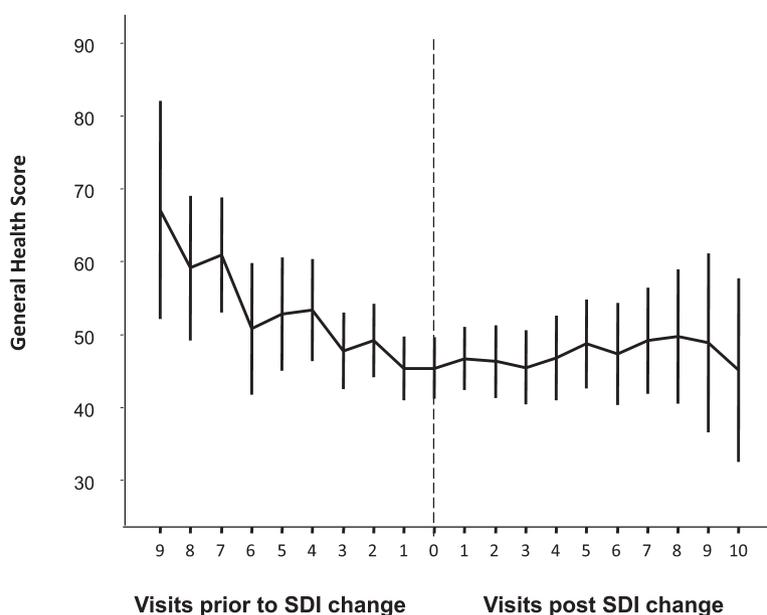


Figure 1. Means (95% CI) for SF-36 General Health subscale scores prior to and post-SDI change. Data trimmed at tails where n < 10 individuals with data. Visits were annual. SF-36: Medical Outcomes Study Short Form-36; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

associated with earlier damage accrual. It is intuitive that the longer a patient lives with a chronic inflammatory disease such as SLE, the more likely he/she will develop damage because of the disease itself, as well as because of medications and comorbidities. Some of the items included in the SDI are seen with increasing frequency in older adults (e.g., osteoporotic fractures, cataracts). Age and disease duration are closely correlated, and one may act as a confounder or proxy for the other. Only age was retained in the final multivariable model because disease duration was no longer statistically significant. However, other studies have clearly demonstrated independent effects of both age and disease

duration on damage accrual, with both variables being retained in multivariable prediction models<sup>13,14</sup>.

Patients with  $\geq 8$  ACR classification criteria for SLE at baseline were more likely to experience earlier damage accrual. This suggests that having multisystem disease increases the likelihood of accumulating organ damage. This may be because of the disease itself, corticosteroid-related, or secondary to more aggressive immunosuppressive pharmacotherapy causing drug-related damage. Indeed, there was an association between immunosuppressive use and earlier damage progression. However, it is unclear whether this correlation was because of toxicities of these medications or

whether their use is a marker of more significant disease. Disease severity and therapeutic exposures in SLE are closely intertwined and their individual effects on damage accrual can be challenging to interpret. However, in multivariable analysis, both the number of ACR criteria at baseline and immunosuppressive use remained statistically significant, suggesting independent effects of both multisystem disease manifestations ( $\geq 8$  ACR criteria) and therapeutic exposures on damage accrual. Other studies have similarly reported earlier damage progression with immunosuppressive use<sup>4</sup>, independent of disease activity or organ involvement.

We did not find an association between either corticosteroid or antimalarial use and change in damage scores. Other studies have shown corticosteroid exposure to be associated with increased damage accrual<sup>2,11,15,16</sup> and antimalarials may be protective<sup>2,11,17,18</sup>. However, confounding is a significant issue in these studies. For example, antimalarials are frequently used in patients with SLE with less active or severe disease, who are thus less at risk for organ damage over time. The association between therapies and damage accrual is complex with competing effects of drug toxicity and better disease control increasing or decreasing the risk for organ damage.

Disease activity, as measured by the mean annual SLEDAI-2K score up to time to first change in SDI, did not correlate with damage progression in our cohort. This contrasts with the findings of other studies that have demonstrated higher levels of disease activity<sup>17,19</sup> and major disease flares<sup>11</sup> to be associated with greater organ damage and earlier damage progression. This may be because these studies used more frequent assessments of disease activity, and thus were more likely to identify disease flares. Interestingly, in our cohort, higher mean ESR and CRP levels up to time to first SDI change were associated with damage progression. Because these 2 markers of inflammation are highly correlated, we chose to include only serum CRP levels in our multivariable analysis where it remained statistically significant. We acknowledge that these biomarkers are nonspecific and their elevation may represent other inflammatory disease processes, including atherosclerosis, which could also contribute to organ damage. Serum CRP levels have traditionally correlated poorly with disease activity in SLE<sup>20</sup>, but studies have refuted this<sup>21,22</sup>. Given the association we have found with earlier damage progression, serum inflammatory biomarkers such as CRP and ESR may be important for identifying patients with SLE at higher risk for organ damage.

Cigarette smoking was associated with earlier progression of organ damage in both univariable and multivariable analyses. Smoking is a known independent risk factor for many of the SDI variables including vascular disease, osteoporosis, and some malignancies. The effect of cigarette smoking on the progression of disease-related damage because of SLE itself remains unclear. There is evidence that

cigarette smoking may interfere with the efficacy of antimalarial therapy, particularly in the treatment of the cutaneous manifestations of SLE<sup>23</sup>. The strong association between cigarette smoking and damage accrual provides further encouragement for patients with SLE to disengage from this lifestyle habit.

The assessment of HRQOL in patients with SLE provides insight into the patients' perspective on their overall disease burden. Several studies have shown that the HRQOL of patients with SLE is lower than that of healthy control subjects<sup>24,25,26,27</sup>. Very few studies have examined how HRQOL is affected by progression of organ damage. The results of our current study indicate that this relationship is complex. For all domains of the SF-36, an increase in damage scores was associated with an initial decline in HRQOL scores. However, following this initial decline, the scores continue to change at the same age-related rate seen in patients without damage progression. A previous study showed a significant decrease in physical functioning scores with concurrent damage, but less of an effect on SF-36 scores with remote or preexisting damage<sup>2</sup>. A possible explanation for both sets of results is patient adaptability to remote damage, while more recent damage may cause a short-term reduction in HRQOL. In our study, this notion of adaptability is best demonstrated by the results for the General Health subscale of the SF-36, where there was evidence of partial recovery in General Health scores following the initial decline that occurred with the acquisition of new damage.

Although the magnitude of the initial decline in SF-36 scores reached statistical significance in most cases, the clinical significance is less clear. In general, changes of 2.5–5.0 in PCS and MCS scores and changes of 5.0–10.0 in SF-36 subscale scores are considered clinically significant<sup>5,28</sup>. Thus, for many of the SF-36 domains, the decline in scores that occurred with a change of 1 in SDI score falls below this threshold for clinical significance. However, extrapolating our results to patients who experience an increase in SDI of multiple units over time, the effect on their SF-36 scores would be multiplied such that there would be a clinically significant effect on HRQOL.

There are some limitations to our study that must be considered in the interpretation of our results. First, this was a single-center cohort with a predominance of whites, which precluded the evaluation of the effect of ethnicity or geographic location on damage progression. This was a prevalent disease cohort, and therefore both patients with newly diagnosed SLE and patients with longstanding SLE were evaluated. Patients without preexisting damage as well as patients with significant organ damage at study entry were included. Because patients were followed annually with a single assessment every 12 months, it was challenging to fully model disease activity that may have varied between visits. While we were able to control for a number of demographic, disease-related, and treatment-related variables

in our analysis of predictors of damage progression, other important variables, including mental health comorbidities and psychosocial factors, could not be evaluated. Thus, we cannot exclude the possibility of residual confounding of our results. Finally, the size of our cohort precluded study of damage accrual in individual organ systems. The study was also underpowered for subgroup analysis based on disease duration or baseline organ damage.

Despite these limitations, our findings provide additional insights into damage accrual and associated risks in patients with SLE. Preexisting organ damage predicts future damage accrual in patients with SLE. Other risk factors, some modifiable, are also associated with earlier damage progression. The negative effect of organ damage progression on HRQOL in patients with SLE underlines the need to address modifiable risk factors and develop effective prevention and treatment strategies to reduce the risk of organ damage over time.

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