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Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort

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ABSTRACT

Objectives: The impact of corticosteroids on the risk of organ damage in the context of clinical end points endorsed in some systemic lupus erythematosus (SLE) clinical trials is underexplored.

Methods: We analysed data from the Hopkins Lupus Cohort using Cox proportional hazards models to understand the impact of exposure to different corticosteroid doses on the risk of developing any new organ damage or any new organ damage at the individual organ systems over time.

Results: Mean prior prednisone dose, recent disease activity and immunosuppressant use during follow-up, as well as organ damage score at cohort entry, were significant independent predictors of the risk of developing any new organ damage. Even after adjustment for recent disease activity, there was a dose-response relationship across the different levels of exposure to prednisone during follow-up and the risk of developing any new organ damage. The risk more than doubled in patients exposed to a mean prior prednisone dose of ≥20 mg/day versus <7.5 mg/day (HR=2.514, p<0.001). It was estimated that a 1 mg/day increase in prior prednisone dose during follow-up was associated with a 2.8% increase in the risk of developing new organ damage. For individual organ systems, exposure to a mean prior prednisone dose of ≥7.5 mg/day versus <7.5 mg/day significantly increased the risk of developing cataracts (HR=2.41, p<0.001), osteoporotic fractures (HR=2.16, p<0.001) and cardiovascular damage (HR=1.54, p=0.041), but showed no significant difference for renal damage (HR=1.44, p=0.163) or for other individual organ systems.

Conclusions: Organ damage in SLE is multifactorial; corticosteroid treatment and disease activity play a role.

KEY MESSAGES

- Organ damage in SLE is multifactorial; both corticosteroid treatment and disease activity play a role.
- A reduction of as little as 1 mg/day in mean prednisone dose reduces the estimated risk of future organ damage by 3%.

INTRODUCTION

Reduction of corticosteroid dose remains an important goal in the management of systemic lupus erythematosus (SLE). Chronic corticosteroid use is associated with the accrual of irreversible organ damage over time, with the highest risk being among those exposed to a mean prednisone dose of ≥20 mg/day.[1 2] A previous analysis from the Hopkins Lupus Cohort demonstrated that the risk of developing later organ damage increases by 50% when patients were exposed to an average cumulative prednisone dose of >6–12 mg/day compared with little to no exposure (>0–6 mg/day) to prednisone.[3] In addition, a similar analysis using the same cohort demonstrated a significant association between corticosteroid use and the risk of developing new cardiovascular damage over time, while controlling for important clinical measures including disease activity, as well as traditional risk factors of cardiovascular diseases.[4]

There are no analyses completed to date that account for either the disease activity score cut-off points or the corticosteroid dose cut-off points endorsed in some of the SLE clinical trials and how those dose levels may translate to the risk of overall organ damage or organ damage at the individual organ systems in SLE.

Therefore, we used Cox proportional hazards models to estimate the impact of different levels of exposure to corticosteroids (as defined by corticosteroid cut-off points

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endorsed in some SLE clinical trials) on the risk of developing any new organ damage or any new organ damage at the individual organ systems over time. Organ damage was measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) or by components of the SDI at the individual organ systems level.

Understanding the association of corticosteroid use by dose to the accrual of organ damage overall and organ damage of individual organ systems over time would help clinicians estimate the long-term benefit gained from the use of corticosteroid-sparing therapies, beyond the benefit gained from controlled disease activity.

METHODS

Data source

The Hopkins Lupus Cohort is a prospective longitudinal study that has followed patients with SLE through quarterly (or more frequent) visits since 1987.[1] All patients are followed by a standardised protocol of disease activity indices (Physician Global Assessment, Lupus Activity Index, and Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA-SLEDAI)) and laboratory tests. The patients with SLE entered into the cohort have provided informed consent, and any use of the cohort's data is done in accordance with the Declaration of Helsinki. Because of its size (more than 2000 patients) and longitudinal design (mean duration of follow-up is ~6 years), the Hopkins Lupus Cohort provides an opportunity to assess the relationship between corticosteroid use and organ damage in this population with relative precision.[4 5]

At the time of this analysis, the cohort included 2265 patients with SLE who were followed over the course of 26 years between 1987 and October 2012, with the average duration of follow-up from cohort entry until lost to follow-up being 6.2 years. Only patients younger than 18 years and those with no follow-up data beyond their initial visit were excluded from this study, rendering the sample size for this analysis at 2199 patients with SLE.

The SDI, a validated instrument designed to measure irreversible organ damage in 12 different organ systems in patients with SLE, was used to identify any new organ damage over time.[6 7] The SDI captures irreversible organ damage, since lupus diagnosis, that is associated with the disease itself, its treatment (including corticosteroid use), or neither. Multiple studies have used the SDI to examine disease variables associated with organ damage.[1 8–12]

The SELENA-SLEDAI was used to measure overall disease activity.[13] The SELENA-SLEDAI score was included in the Cox proportional hazards model as a two-level variable. A predefined cut-off point of 6 was selected based on what has been endorsed for SELENA-SLEDAI entry criteria in some SLE clinical trials. Similarly, the cut-off point for prednisone dose was selected at 7.5 mg/day; however, a few additional prednisone cut-off points were also evaluated.

Statistical analysis

Baseline demographics and clinical characteristics were analysed for the overall study sample (N=2199) and for subgroups of patients with SELENA-SLEDAI score <6 (N=1643) and SELENA-SLEDAI score ≥6 (N=528) at baseline. The rate of any organ damage and the rate of any organ damage at the individual organ systems, as well as the rate of first occurring new organ damage and the rate of first occurring new organ damage at the individual organ systems, during follow-up were calculated.

A Cox proportional hazards model was developed to assess the relationship between mean prior prednisone dose during follow-up and the risk of developing any new organ damage or organ damage at the individual organ systems (ie, cataracts, osteoporotic fractures, cardiovascular damage and renal damage) since cohort entry. The Cox model only accounts for first occurrence of new organ damage or first occurrence of new organ damage at the individual organ systems during follow-up. Time-invariant and time-dependent variables were included in the model. To precisely assess the impact of time-dependent variables (recent disease activity and prior prednisone dose) on the risk of organ damage, we reformatted the data set to consist of one record for each quarter (ie, person-quarter record), which is consistent with the cohort's data collection frequency set by the Hopkins Lupus Cohort protocol (ie, quarterly). For each person-quarter record (which was set as a fixed date at the last day of each quarter in a given year) time-dependent variables were recorded based on the most recent visit record prior to each person-quarter record. These time-dependent variables included mean prior daily prednisone dose (calculated as the average prednisone dose during prior cohort follow-ups from cohort entry up to the most recent visit prior to each person-quarter record); recent SELENA-SLEDAI score (updated for each person-quarter record, based on the most recent visit prior to each person-quarter record); immunosuppressant use (updated for each person-quarter record, based on whether a patient has been on an immunosuppressant any time during follow-up from cohort entry up to the most recent visit prior to each person-quarter record); antimalarial use (updated for each person-quarter record, based on whether a patient has been on an antimalarial any time during follow-up from cohort entry up to the most recent visit prior to each person-quarter record); recent body mass index (based on the most recent visit prior to each person-quarter record); and recent cholesterol level (based on the most recent visit prior to each person-quarter record). The history of comorbid conditions (ie, hypertension, diabetes and renal damage) was recorded based on the absence or presence of these conditions prior to each person-quarter record. A flare, which is a measure of acute change in disease activity, was not included in the model as it is highly collinear with the time-dependent disease activity variable of 'SELENA-SLEDAI score' that is updated at each person-quarter record.

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For the overall model estimating the risk for developing any new organ damage over time, patients were followed from cohort entry until one of the following end points (whichever occurred first): (1) 826 patients were followed until the date the first irreversible organ damage occurred; (2) 1304 were censored at the date when the patient dropped from the cohort; and (3) 67 were censored at 15 years after cohort entry.

For the cataract model, patients were followed from cohort entry until one of the following end points (whichever occurred first): (1) 196 patients were followed until the date the first cataract event occurred; (2) 1831 were censored at the date when the patient dropped from the cohort; and (3) 170 were censored at 15 years after cohort entry.

For the cardiovascular model, patients were followed from cohort entry until one of the following end points (whichever occurred first): (1) 128 patients were followed until the date the first cardiovascular event occurred; (2) 1887 were censored at the date when the patient dropped from the cohort; and (3) 182 were censored at 15 years after cohort entry.

For the fracture model, patients were followed from cohort entry until one of the following end points (whichever occurred first): (1) 177 patients were followed until the date the first fracture event occurred; (2) 1843 were censored at the date when the patient dropped from the cohort; and (3) 177 were censored at 15 years after cohort entry.

For the renal model, patients were followed from cohort entry until one of the following end points (whichever occurred first): (1) 75 patients were followed until the date the first renal damage occurred; (2) 1927 were censored at the date when the patient dropped from the cohort; and (3) 195 were censored at 15 years after cohort entry.

For the overall model estimating the risk for developing any new organ damage or for any of the models of individual organ systems, the analysis was truncated at 15 years of follow-up after cohort entry because less than 10% of patients had a follow-up longer than 15 years.

Furthermore, since the study sample included in this analysis (N=2199) is not fully an inception sample (29.2% entered the Hopkins cohort within the 1st year of diagnosis, 37.8% between 1–5 years of diagnosis and 33.0% after 5 years of diagnosis), and the analyses completed did not account for corticosteroid exposure prior to cohort entry, a sensitivity analysis for the overall model estimating the risk for developing any new organ damage over time was repeated using the proportion of patients who have entered the Hopkins cohort within the 1st year (n=642, 29.2%) and within the 2nd year (n=944, 42.9%) of their SLE diagnosis.

RESULTS

Baseline demographics and clinical characteristics

Demographic and disease characteristics at cohort entry are summarised in table 1. At cohort entry, the mean age of the study sample was 38.0 years. The mean duration of SLE was 5.1 years, with 29.2% of patients entering the cohort within their 1st year of diagnosis and 42.9% of patients entering the cohort within their 2nd year of diagnosis. Of the 2199 patients with SLE, 92.5% were female, 55.3% were white and 37.6% were black. The treatment profiles at cohort entry included 19.2% of patients receiving an immunosuppressant drug, 70.3% receiving hydroxychloroquine, and 52.7% receiving corticosteroids (of which 40.2% were receiving a prednisone dose ≥7.5 mg/day). Patients could be receiving more than one type of SLE treatment at cohort entry. The average overall SELENA-SLEDAI score at cohort entry was 3.5 (of which 24.3% had a SELENA-SLEDAI score ≥6). Only 50.5% of the study sample had any type of organ damage at cohort entry, with a mean SDI score of 1.2.

Distribution of the rate of any organ damage and any organ damage at the individual organ systems during follow-up

Overall, the most frequent types of organ damage occurring over time were musculoskeletal damage (20.3%) and ocular damage (15.8%) (table 2). Osteoporotic fractures represented 12.4% of the total number of organ damage events, while cataracts represented 13.7% of the total number of organ damage events. When assessing the rates of first organ damage events by organ system, the number of events for musculoskeletal damage (20.3%) and ocular damage (16.3%) were the highest. This result suggested that these corticosteroid-related comorbidities might present prior to any other type of organ damage in patients with SLE over time.

Cox proportional hazards models for any new organ damage

From the Cox proportional hazards models, age at cohort entry, SDI score at cohort entry, mean prednisone dose during follow-up, recent SELENA-SLEDAI score during follow-up, year of SLE diagnosis and immunosuppressant use during follow-up were significant predictors of any new organ damage ($p<0.05$) (table 3). From a preliminary Cox proportional hazards model, not included in this paper, we demonstrated that neither SELENA-SLEDAI score at cohort entry nor immunosuppressant use at cohort entry were significant predictors of any new organ damage over time and, therefore, were not included in the final models.

From Model 1, patients exposed on average to prior prednisone dose ≥7.5 mg/day over time had 1.742 times the risk of developing any new organ damage as compared with those exposed on average to prior prednisone dose <7.5 mg/day (HR=1.742, $p<0.001$) (table 3). From Model 2, the estimated risk of developing any new organ damage over time increased linearly as the exposure to a higher mean prior prednisone dose increased over time. The subgroup of patients exposed on average to prior prednisone dose ≥20 mg/day over time had more than two times the risk of developing any new organ damage, as compared with

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Table 1 Baseline characteristics of the study cohort

Baseline characteristics	All patients (N=2199)	SELENA-SLEDAI <6 (N=1643)	SELENA-SLEDAI ≥6 (N=528)
Mean age, years	32.9	33.8	30.1
Mean age at cohort entry, years	38.0	39.0	35.2
Gender, n (%)			
Male	165 (7.50)	126 (7.67)	37 (7.01)
Female	2034 (92.50)	1517 (92.33)	491 (92.99)
Race, n (%)			
White	1215 (55.25)	965 (58.73)	232 (43.94)
Black	827 (37.61)	558 (33.96)	261 (49.43)
Asian	74 (3.37)	58 (3.53)	15 (2.84)
Other	83 (3.77)	62 (3.77)	20 (3.79)
Mean SDI score at cohort entry	1.2	1.1	1.3
Mean SELENA-SLEDAI score at cohort entry	3.5	1.7	9.2
Prednisone use at cohort entry, n (%)*			
Yes	1144 (52.72)	755 (46.04)	387 (73.30)
No	1026 (47.28)	885 (53.96)	141 (26.70)
Year of SLE diagnosis, n (%)			
Pre-1980s	143 (6.50)	98 (5.96)	44 (8.33)
1980s	408 (18.55)	270 (16.43)	134 (25.38)
1990s	826 (37.56)	621 (37.80)	190 (35.98)
2000s	822 (37.38)	654 (39.80)	160 (30.30)
Time since SLE diagnosis			
Mean, years	5.1	5.2	5.1
<1, n (%)	642 (29.20)	478 (29.09)	154 (29.17)
1–5, n (%)	831 (37.79)	641 (39.01)	179 (33.90)
>5, n (%)	726 (33.02)	524 (31.89)	195 (36.93)
Follow-up, years, (n %)			
<1	489 (22.24)	374 (22.76)	111 (21.02)
1–5	687 (31.24)	530 (32.26)	151 (28.60)
5–10	489 (22.24)	374 (22.76)	103 (19.51)
>10	534 (24.28)	365 (22.22)	163 (30.87)
Mean follow-up, years	6.2	5.9	7.2
Mean dropout rate per year, %	16.1	17.1	13.9

*Data were not available for all 2199 patients.
SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; SLE, systemic lupus erythematosus.

those exposed on average to prior prednisone dose <7.5 mg/day (HR=2.514, p<0.001).

In Model 3, we handled mean prior prednisone dose during follow-up as a continuous variable, rather than categorical, to further investigate the dose-response relationship between mean prior prednisone dose and the risk of developing any new organ damage over time (table 3). With every 1 mg increase in average daily prednisone dose, irrespective of baseline prednisone dose, the risk of developing any new organ damage increased by approximately 3% (HR=1.028, p<0.001), which translates to a 15% (HR=1.150, 95% CI 1.112 to 1.188, p<0.001) increased risk associated with an average of a 5 mg/day increase in prior prednisone dose.

When the Model 1 analysis was restricted to patients who entered the Hopkins cohort within a year or two of their SLE diagnosis (Models 4 and 5), the main findings were similar to those seen with the full cohort in Model 1 (table 4).

Cox proportional hazards models at the individual organ systems

We further examined the impact of different levels of exposure to prior prednisone on the risk of developing any new organ damage at the individual organ systems, as defined by the 12 components of the SDI. In this paper, we report only the models of four individual types of organ damage (ie, cataracts, osteoporotic fractures, cardiovascular damage and renal damage) (table 5).

For the cataract model, mean prior prednisone dose during follow-up (HR=2.412, p<0.001) and recent SELENA-SLEDAI score during follow-up (HR=1.475, p=0.045) were significantly positively associated with the risk of developing cataracts in this relatively young patient population (table 5). The osteoporotic fracture model was consistent with the finding from the cataract model, in that the risk of osteoporotic fractures was driven by mean prior prednisone dose during follow-up; however, in this model, the relationship between

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Table 2 Distribution of any and first organ damage and organ damage by organ system during follow-up

	Any organ damage N (%)	First organ damage N (%)
Any organ damage (total)	1428 (100.0)	826 (100.00)
Ocular damage	225 (15.76)	135 (16.34)
Cataract damage	196 (13.73)	116 (14.04)
Neuropsychiatric damage	191 (13.38)	128 (15.50)
Stroke	57 (3.99)	28 (3.39)
Renal damage	75 (5.25)	51 (6.17)
Pulmonary damage	165 (11.55)	94 (11.38)
Pulmonary fibrosis	90 (6.30)	48 (5.81)
Cardiovascular damage	128 (8.96)	55 (6.66)
Peripheral damage	46 (3.22)	21 (2.54)
Gastrointestinal damage	77 (5.39)	51 (6.17)
Musculoskeletal damage	290 (20.31)	168 (20.34)
Osteoporotic fracture damage	177 (12.39)	88 (10.65)
Skin damage	32 (2.24)	21 (2.54)
Gonadal failure damage	30 (2.10)	19 (2.30)
Diabetes damage	60 (4.20)	24 (2.91)
Malignancy damage	109 (7.63)	59 (7.14)

SELENA-SLEDAI score during follow-up and risk of damage was not significant. Being female versus male (HR=2.32, p=0.015) or white versus black (HR=1.89, p<0.001) almost doubled the risk of developing osteoporotic fractures in this patient population. When using corticosteroid as a continuous variable, an increase of prior prednisone dose as minimal as 1 mg/day (irrespective of baseline prednisone dose) was shown to significantly increase the risk of cataracts by 3.8% and osteoporotic fractures by 4.2% (data not shown).

Table 3 Time-dependent Cox proportional hazards models for any organ damage

	Model 1		Model 2		Model 3	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age at cohort entry	1.032 (1.026 to 1.038)	<0.001	1.033 (1.027 to 1.039)	<0.001	1.032 (1.026 to 1.038)	<0.001
Sex (female vs male)	1.071 (0.833 to 1.377)	0.592	1.089 (0.847 to 1.400)	0.508	1.080 (0.840 to 1.388)	0.550
Race						
Black (vs White)	1.113 (0. 963 to 1.286)	0.149	1.109 (0.960 to 1.282)	0.161	1.132 (0.980 to 1.307)	0.091
Asian (vs White)	0.894 (0.541 to 1.476)	0.661	0. 897 (0.543 to 1.482)	0.672	0.908 (0.550 to 1.499)	0.705
Other (vs White)	0.879 (0.559 to 1.382)	0.576	0.870 (0.553 to 1.368)	0.545	0.882 (0.561 to 1.387)	0.587
Year of SLE diagnosis	0.992 (0.984 to 1.000)	0.044	0.991 (0.983 to 0.998)	0.018	0.989 (0.981 to 0.997)	0.005
SDI at cohort entry	1.064 (1.023 to 1.106)	0.002	1.064 (1.024 to 1.107)	0.002	1.064 (1.023 to 1.107)	0.002
SELENA-SLEDAI score during follow-up (≥6 vs <6)	1.398 (1.170 to 1.670)	<0.001	1.370 (1.146 to 1.638)	<0.001	1.374 (1.149 to 1.642)	<0.001
Immunosuppressant use during follow-up (yes vs no)	1.225 (1.046 to 1.434)	0.012	1.209 (1.032 to 1.417)	0.019	1.246 (1.068 to 1.455)	0.005
Antimalarial use during follow-up (yes vs no)	0.926 (0.801 to 1.071)	0.299	0.958 (0.827 to 1.109)	0.566	0.964 (0.832 to 1.116)	0.623
Mean prior prednisone dose, mg/day*						
(≥7.5 vs <7.5)	1.742 (1.489 to 2.039)	<0.001	NA		NA	
(≥7.5–<15 vs <7.5)	NA		1.537 (1.284 to 1.840)	<0.001	NA	
(≥15–<20 vs <7.5)	NA		1.799 (1.350 to 2.399)	<0.001	NA	<0.001
(≥20 vs <7.5)	NA		2.514 (1.977 to 3.196)	<0.001	NA	
1 mg/day	NA		NA		1.028 (1.022 to 1.035)	

*We calculated the time-varying predictor 'mean prior prednisone dose' as the average prednisone dose during prior cohort follow-up.
NA, not applicable; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; SLE, systemic lupus erythematosus.

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Table 4 Time-dependent Cox proportional hazards models for any organ damage for inception cohort (patients within the 1st year of diagnosis (N=642) and patients within the 2nd year of diagnosis (N=944))

	Model 4 (N=642)		Model 5 (N=944)	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at cohort entry	1.043 (1.031 to 1.056)	<0.001	1.037 (1.027 to 1.047)	<0.001
Sex (female vs male)	1.033 (0.674 to 1.583)	0.882	1.069 (0.759 to 1.506)	0.702
Race				
Black (vs White)	1.067 (0. 809 to 1.407)	0.647	1.140 (0.911 to 1.426)	0.253
Asian (vs White)	1.041 (0.455 to 2.383)	0.924	0. 734 (0.324 to 1.663)	0.459
Other (vs White)	1.176 (0.468 to 2.957)	0.730	1.366 (0.726 to 2.569)	0.334
Year of SLE diagnosis	0.979 (0.957 to 1.003)	0.080	0.986 (0.967 to 1.006)	0.164
SDI at cohort entry	1.043 (0.943 to 1.155)	0.411	1.050 (0.968 to 1.140)	0.241
SELENA-SLEDAI score during follow-up (≥6 vs <6)	1.382 (0.960 to 1.989)	0.082	1.328 (0.986 to 1.789)	0.062
Immunosuppressant use during follow-up (yes vs no)	1.326 (0.969 to 1.815)	0.078	1.424 (1.103 to 1.837)	0.007
Antimalarial use during follow-up (yes vs no)	0.916 (0.698 to 1.201)	0.525	0.923 (0.734 to 1.160)	0.491
Mean prednisone dose, mg/day (≥7.5 vs <7.5)	1.834 (1.339 to 2.512)	<0.001	1.730 (1.338 to 2.236)	<0.001

NA, not applicable; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; SLE, systemic lupus erythematosus.

Alternately, from the cardiovascular and the renal models, SELENA-SLEDAI score during follow-up was shown to have a greater impact on risk, as compared with mean prior prednisone dose during follow-up (table 5).

DISCUSSION

To our knowledge, this is the first study that quantifies the risk of corticosteroid use on overall organ damage or individual organ damage by dose cut-off points endorsed in some SLE clinical trials. This analysis is of significance when attempting to understand the long-term benefit of corticosteroid-sparing agents in the clinical setting. Overall, this study confirmed what has been previously reported on the increased risk of irreversible organ damage associated with corticosteroid use in SLE.[2] The most important finding of this study was the dose-response relationship between mean prior prednisone dose during follow-up and the risk of developing irreversible organ damage over time. Patients who received, on average, higher prednisone doses (≥7.5 mg/day) during follow-up were significantly more likely to develop any new organ damage over time, compared with those who were exposed, on average, to prednisone doses <7.5 mg/day after adjustment for disease activity and other variables. Patients in the highest dose subgroup (prednisone dose ≥20 mg/day) were more than twice more likely to experience organ damage than those who received <7.5 mg/day (HR=2.514; p<0.001). Significant predictors of organ damage other than mean prior prednisone dose during follow-up (HR=1.742; p<0.001) were recent SELENA-SLEDAI score during follow-up (HR=1.398, p<0.001); immunosuppressant use during follow-up (HR=1.225; p=0.012); SDI score at cohort entry (HR=1.064; p=0.002); age at cohort entry (HR=1.032; p<0.001); and year of SLE diagnosis (HR=0.992; p=0.044) (Model 1). The sensitivity analyses completed using the inception cohort(s) were consistent with the findings of the overall model (N=2199) for any new organ damage, where corticosteroid was a significant predictor of the risk of any new organ damage over time while adjusting for important confounders (table 4).

Previous analysis from the Hopkins Lupus Cohort has demonstrated a reduced risk of organ damage associated with average cumulative doses of prednisone <6 mg/day.[3] In this analysis, we estimated the impact of average prednisone dose as a continuous variable (rather than a discrete variable) and we quantified the risk associated with an increase in average daily prednisone dose of 1 mg/day (HR=1.028; p<0.001), irrespective of baseline prednisone dose (table 3). These data on the risk of damage associated with an increase in average prednisone dose of 1 mg/day and 5 mg/day (HR=1.150, p<0.001) may help inform the clinical decision-making process for corticosteroid dose tapering in SLE. Successful corticosteroid tapering below levels of 5 mg/day is possible with low levels of disease activity (SELENA-SLEDAI 0–2),[5] highlighting the significantly great unmet need for corticosteroid-sparing therapies that simultaneously reduce disease activity in SLE.

Another significance of this study is that it demonstrates the risk associated with corticosteroids on individual organ systems within the same study cohort, which further provides insight into the types of damage that are more likely to occur first over time. Daily prednisone doses ≥7.5 mg increased the risk of developing cataracts, osteoporotic fractures and cardiovascular damage, but not renal damage. The relative impact of corticosteroid use on cataracts, osteoporotic fractures and cardiovascular damage varied as is evident by the different effect size values (HR values) for these different types of organ damage (table 5). The effect size value was higher for cataracts than for osteoporotic fractures and for cardiovascular damage.

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Table 5 Time-dependent Cox proportional hazards models for cataracts, osteoporotic fractures, cardiovascular damage and renal damage

Parameter	HR (95% CI)	p Value
Cataracts		
Age at cohort entry	1.065 (1.053 to 1.077)	<0.001
Sex		
Female vs Male	1.549 (0.892 to 2.691)	0.120
Race		
Black vs White	1.045 (0.771 to 1.416)	0.775
Asian vs White	1.449 (0.632 to 3.325)	0.381
Other vs White	0.919 (0.336 to 2.517)	0.870
SDI at cohort entry	1.004 (0.923 to 1.091)	0.931
Year of SLE diagnosis	1.012 (0.995 to 1.028)	0.157
Mean prior prednisone dose during follow-up, mg/day		
≥7.5 vs <7.5	2.412 (1.778 to 3.273)	<0.001
SELENA-SLEDAI score		
≥6 vs <6	1.475 (1.008 to 2.157)	0.045
Osteoporotic fractures		
Age at cohort entry	1.042 (1.030 to 1.055)	<0.001
Sex		
Female vs Male	2.320 (1.174 to 4.585)	0.015
Race		
Black vs White	0.529 (0.379 to 0.740)	<0.001
Asian vs White	0.438 (0.108 to 1.783)	0.249
Other vs White	1.074 (0.434 to 2.659)	0.877
SDI at cohort entry	1.043 (0.958 to 1.136)	0.332
Year of SLE diagnosis	0.992 (0.975 to 1.010)	0.378
Immunosuppressant use		
Yes vs No	1.490 (1.078 to 2.059)	0.016
Mean prior prednisone dose during follow-up (mg/day)		
≥7.5 vs <7.5	2.161 (1.546 to 3.022)	<0.001
SELENA-SLEDAI score		
≥6 vs <6	1.055 (0.676 to 1.646	0.813
Cardiovascular damage		
Age at cohort entry	1.048 (1.032 to 1.063)	<0.001
Sex		
Female vs Male	0.531 (0.306 to 0.924)	0.025
Race		
Black vs White	0.854 (0.569 to 1.284)	0.449
Asian vs White	2.875 (1.129 to 7.317)	0.027
Other vs White	1.169 (0.359 to 3.802)	0.796
SDI at cohort entry	1.166 (1.067 to 1.273)	<0.001
Year of SLE diagnosis	0.984 (0.964 to 1.004)	0.112
Mean prior prednisone dose during follow-up, mg/day		
≥7.5 vs <7.5	1.544 (1.018 to 2.341)	0.041
SELENA-SLEDAI score		
≥6 vs <6	2.737 (1.780 to 4.209)	<0.001
Antimalarials		
Yes vs No	0.898 (0.605 to 1.333)	0.593
Hypertension		
Yes vs No	2.322 (1.267 to 4.257)	0.006
Diabetes		
Yes vs No	0.832 (0.257 to 2.689)	0.758
Renal damage		
Yes vs No	2.229 (1.133 to 4.384)	0.020
BMI	1.005 (0.981 to 1.030)	0.668
Cholesterol	1.004 (1.000 to 1.007)	0.039
Renal damage		
Age at cohort entry	0.998 (0.978 to 1.017)	0.814

Continued

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Table 5 Continued

Parameter	HR (95% CI)	p Value
Sex		
Female vs Male	0.595 (0.288 to 1.226)	0.159
Race		
Black vs White	1.694 (1.023 to 2.804)	0.041
Asian vs White	1.547 (0.361 to 6.626)	0.556
Other vs White	3.347 (1.130 to 9.911)	0.029
SDI at cohort entry	1.126 (1.010 to 1.255)	0.032
Year of SLE diagnosis	0.974 (0.950 to 0.998)	0.036
Immunosuppressant use		
Yes vs No	1.040 (0.623 to 1.737)	0.879
Mean prior prednisone dose during follow-up, mg/day		
≥7.5 vs <7.5	1.440 (0.863 to 2.403)	0.163
SELENA-SLEDAI score		
≥6 vs <6	4.079 (2.521 to 6.600)	<0.001
Antimalarials		
Yes vs No	0.449 (0.270 to 0.749)	0.002
Hypertension		
Yes vs No	2.157 (0.912 to 5.102)	0.080

BMI, body mass index; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; SLE, systemic lupus erythematosus.

When evaluating mean prednisone dose as a continuous measure for the cataract and osteoporotic fracture models, we estimated that an increase in average prednisone dose of 1 mg/day was associated with the increased risk of cataracts by 3.8% and osteoporotic fractures by 4.2%. Furthermore, our data demonstrated that the most frequent types of organ damage to first occur over time were musculoskeletal damage and ocular damage (cataracts), the rates of which may potentially be attenuated by the use of corticosteroid-sparing agents in SLE (table 2).

The findings from this study are representative of a well-controlled patient population with SLE (mean SELENA-SLEDAI score at baseline was 3.5) with relatively lower exposure to corticosteroids over time. We do not know how these data may compare with other patients with SLE across the USA; however, we believe that the results of this study may represent one of the most conservative estimates of the rates of organ damage in SLE to date, given the smaller percentage of patients receiving higher doses on prednisone (≥7.5 mg/day) over time (from the Hopkins cohort, the proportion of patients on prednisone ≥7.5 mg/day had declined from 57.4% since 1987 to 11.2% as of 2012). Furthermore, there are short-term side effects associated with varied levels of exposure to corticosteroids that were not explored in this study, including the risk of infections. Considering all these factors together, the burden imposed by corticosteroid use in SLE is important. Clearly, there is an urgent need for corticosteroid-sparing therapies that also better control SLE disease activity. A reduction of as little as 1 mg/day or 5 mg/day in mean prednisone dose would have benefits and potential healthcare savings based on our analyses. Evaluation of non-corticosteroid therapies that manage disease activity and symptoms but avoid the adverse effects of corticosteroids (including but not limited to organ damage) is required to improve the treatment of patients with SLE. Corticosteroid-sparing agents would potentially decrease the risk of these corticosteroid-related comorbidities in a rather young patient population and subsequently decrease the healthcare costs needed to manage these conditions over time.

There are limitations to this study. In the Hopkins Lupus Cohort, measures of treatment adherence or compliance between quarterly patients' visits were not available; thus, our analyses were based on the assumption that the corticosteroid dose was constant for the quarter after each person-quarter record. Furthermore, the analyses were based on the assumption that those who are censored are not different, on average, from those who are not censored with respect to the relationship between predictors and damage rates, after adjustment for other variables in the Cox models. This seems like a reasonable assumption given the fact that dropouts occur for many reasons. However, if this assumption does not hold, our estimates could be somewhat biased.

Disease activity is a predictor of damage, and prednisone reduces disease activity; therefore, prednisone might have some benefit on preventing some types of organ damage due to SLE alone. For this reason, the HRs reported, while clinically important, are not pure estimates of the impact of prednisone.

In conclusion, understanding the overall risk of organ damage and risk at individual organ systems associated with exposure to high-dose prednisone over time (ie, ≥7.5 mg/day) and further understanding the risk imposed by an average of a 1 mg/day or 5 mg/day

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increase in prednisone dose would help clinicians better understand the long-term benefit gained from the use of corticosteroid-sparing therapies that are currently in development in SLE clinical trials.

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