Published in final edited form as:
Ann Rheum Dis. 2008 June ; 67(6): 829–834. doi:10.1136/ard.2007.077594.

Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV)

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Abstract

Objective—To examine the predictors of time-to-seizure occurrence and their impact on damage accrual and mortality in LUMINA, a multiethnic (Hispanic, African American and Caucasian) cohort of patients with systemic lupus erythematosus.

Methods—Seizures were defined as per the American College of Rheumatology (ARC) nomenclature and case definitions for neuropsychiatric lupus syndromes. Factors associated with time-to-seizure occurrence occurring at or after diagnosis (TD) of systemic lupus erythematosus were examined by univariable and multivariable Cox proportional hazard regression analyses. The impact of seizures on damage accrual and mortality was also examined by multivariable analyses after adjusting for variables known to affect these outcomes.

Results—A total of 600 patients were included in these analyses. Of them, 40 (6.7%) developed seizures at or after TD; by multivariable analyses, disease activity and younger age were independent predictors of a shorter time-to-seizure occurrence (HR = 1.10 and 1.04; 95% CI 1.04 to 1.15 and 1.00 to 1.08, p = 0.0004 and 0.0304, respectively) whereas mucocutaneous involvement (HR = 0.34, 95% CI 0.16 to 0.41, p = 0.0039) and hydroxychloroquine use (HR = 0.35, 95% CI 0.15 to 0.80, p = 0.0131) were independent predictors of a longer time-to-seizure occurrence. Seizures were an independent contributor to damage accrual but not to mortality.

Conclusions—Seizures tend to occur early in the course of systemic lupus erythematosus, and contribute to damage accrual. Younger age and disease activity are independent predictors of a shorter time-to-seizure occurrence; antimalarials appear to have a protective role in seizure occurrence.

Neuropsychiatric manifestations of systemic lupus erythematosus (SLE) comprise a complex array of neurological, psychiatric and behavioural manifestations. Seizures are probably one of the most ominous and relevant clinical expressions of damage accrual in SLE,[1] hence, of its long-term prognosis.

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Competing interests: None.

Different mechanisms of nervous tissue injury have been described in SLE but a precise one is yet to be elucidated. Indeed, the secretion of pro-inflammatory cytokines (such as interleukin 1 and 6, and tumour necrosis factor-α) leads to the activation of the hypothalamic—pituitary—adrenal axis with the consequent reduction of the seizure threshold.[2-4] In this setting of ongoing inflammation, anti-neuronal antibodies have been recognised in the serum of patients with SLE suffering from neurological manifestations such as encephalopathies and seizures.[2 5] Focal ischaemia and/or infarcts resulting from vascular occlusion secondary to thrombosis, embolism, vasculopathy or haemorrhage are also recognised as possible causative factors of seizures in SLE.[2 6] Furthermore, these patients may experience other clinical events that may increase their risk of developing seizures and the occurrence of seizures may associate with other serious clinical events. Given these evidences, we decided to examine the factors associated with time-to-seizure occurrence, as a primary manifestation of SLE, in LUMINA, a large multiethnic cohort. We hypothesised that patients with other serious disease manifestations and higher levels of disease activity will experience seizures early in the course of their disease and that seizures will contribute to damage accrual and mortality.

PATIENTS AND METHODS

Patients

The LUMINA cohort has been previously described.[7] Briefly, LUMINA is a longitudinal outcome study of patients with SLE from three different ethnic groups (Hispanic (of Mexican and Central American (Texan) or Puerto Rican ancestry), African American and Caucasian), being conducted at three institutions (The University of Alabama at Birmingham, The University of Texas Health Science Center at Houston and The University of Puerto Rico Medical Sciences Campus). This study was approved by the Institutional Review Boards for the Protection of Human Subjects of these institutions and is conducted according to the Declaration of Helsinki's guidelines.

Patients meeting four American College of Rheumatology (ACR) revised and updated criteria for SLE,[8 9] ≥16 years of age, with disease duration ≤5 years at study entry, who are followed-up at any of the institutions are eligible for inclusion. Patients are seen at recruitment or baseline (T0), at 6 and 12 months (T0.5 and T1, respectively) and yearly thereafter (T2, T3, etc. to TL (last visit)). Cumulative data prior to enrolment in the cohort are obtained from the patients' medical records. All visits include medical records review, interviews and questionnaires, physical examination, and ancillary laboratory studies. The time of diagnosis is defined as the time at which patients meet four of the ACR criteria for SLE (TD, herein).

Seizures were defined either by self-report, if observed by a reliable witness and reported to the study physician during the interview, or if they were documented in the medical records available during the visit if occurring at any time at or after TD and were attributable to SLE. Imaging or electrophysiological studies were not required as they were not part of the LUMINA protocol. This definition was based on the ACR nomenclature and case definitions for neuropsychiatric lupus syndromes.[10] Patients who developed seizures not attributable to SLE (uncontrolled hypertension, uraemia, ketoacidosis, electrolyte imbalances, infections or medications) were excluded.

Variables

As described previously, the LUMINA database includes variables from the socio-economic—demographic, clinical, immunological, genetic and behavioural and psychological domains. All other variables are measured at T0 and at every subsequent visit except for the genetic variables, which are only obtained at T0. Only variables included in this study will be described.

Variables from the socio-economic—demographic domain included were age, ethnicity, education, poverty (as defined by the US Federal government adjusted for the number of subjects in the household),[11] marital status, health insurance and health-related behaviours (smoking, drinking, not exercising and using recreational drugs).

Clinical variables included were disease duration (TD-T0), follow-up time (T0-TL), total disease duration (TD-TL), disease manifestations, disease activity and damage, ancillary laboratory tests and medications usage. TL was the time at which seizures occurred for those patients who developed them; thus, the observation time for them was truncated at this time.

Disease activity was ascertained with the Systemic Lupus Activity Measure-Revised (SLAM-R)[12] at TD, T0 and TL; in addition, the SLAM-R average or the arithmetic mean of this score for all available study visits plus the SLAM-R obtained at TD was computed. An average SLAM-R weighted with the time interval between visits was also calculated to capture disease activity over time. Seizures were excluded from the SLAM-R at all times in order to avoid attributing any disease activity to them.

Damage accrual was measured with the Systemic Lupus International Collaborating Clinics (SLICC)[13] Damage Index (SDI) at T0 and TL Damage was examined as a discrete numeric variable (total damage score) but seizures were excluded from the SDI for this study.

Laboratory variables at T0 such as total cholesterol (high >200 mg/dl), low-density lipoprotein (LDL) cholesterol (calculated using the Friedewald formula (high >130 mg/dl)), high-density lipoprotein (HDL) cholesterol (low <35 mg/dl), triglyceride levels (high >205 mg/dl) and serum C-reactive protein (measured as high-sensitivity C-reactive protein by immunometric assay, Immulite 2000 Diagnostic Products Corporation, Los Angeles, CA, USA (high >16.5 mg/l)) were recorded as well as the presence of autoantibodies, including antinuclear antibodies (by immunofluorescence using HEp-2 cell line), anti-double-stranded DNA (anti-dsDNA, by immunofluorescence against *Crithidia luciliae* (abnormal ≥1:10), anti-Smith, anti-La and anti-Ro (by counter immunoelectrophoresis against human spleen and calf thymus extract).[14,15] IgG and IgM antiphospholipid antibodies ((aPL, abnormal >13 GPL U/ml and/or >13 MPL U/ml) by enzyme immunoabsorbent assay (ELISA) technique)[16] and the lupus anticoagulant (Staclot Test Diagnostica Stago 92600, Asnières-Sur-Seine, France).[17]

Cumulative exposure to glucocorticoids, hydroxychloroquine, methotrexate, cyclophosphamide and azathioprine were also recorded. Glucocorticoid exposure was estimated based on the current daily dose reported at each study visit and the duration between visits as an average daily dose weighted by the time between visits.

Statistical analyses

First, variables from the different domains were examined as potential predictors of time-to-seizure occurrence by Cox univariable proportional hazards regressions; the final multivariable Cox regression model included age, gender, ethnicity and those variables with $p \leq 0.10$ in the univariable Cox regressions; the results are presented as hazard ratios (HR) where values ≥1 indicate a shorter time-to-seizure occurrence and values <1 indicate a longer time.

Damage was examined by a multivariable Poisson regression model and mortality with a Cox proportional hazard regression model; in both cases, the observation time for all patients was the last actual visit on record. Age, gender, ethnicity and variables previously found to be important contributors to these outcomes were included in these models.[1,18,19] Specific domains and items of the SDI in those patients who developed seizures and those who did not were examined by the χ^2 distribution. Analyses were performed using SAS, version 9.1 (Cary, NC, USA).

RESULTS

At the time these analyses were performed the LUMINA cohort consisted of 631 patients. Thirty-one of them were excluded from the analyses because they either developed seizures prior to TD (n = 9) or seizures were not attributable to lupus (n = 22); thus, 600 patients (89.8% women) were included in these analyses; 40 (6.7%) of them had developed seizures at or after TD and were attributable to lupus. Nearly two-thirds of these patients (62.5%) developed seizures within 1 year of SLE diagnosis, but seizures continue to occur over the follow-up; in fact, one patient developed seizures 8 years after TD. All ethnic groups were represented (Hispanic-Texan: 18.8%, Hispanic-Puerto Rican: 28.0%, African-American: 36.3%, Caucasian: 16.8%). The patients' mean (SD) age at T0 was 36.5 (12.6) years; mean (SD) disease duration (TD-T0) for the entire group was 17.3 (16.1) months (range: 0.2–60.0).

Features associated with time to seizure occurrence

Univariable analyses

Socio-economic-demographic features: As noted in table 1, African-American ethnicity was associated with a shorter time-to-seizure occurrence (HR = 5.37; 95% CI 1.26 to 22.87, p = 0.0231), whereas Texan-Hispanic ethnicity was only of borderline statistical significance (HR = 4.12; 95% CI 0.89 to 19.12, p = 0.0736). Younger age was also associated with a shorter time-to-seizure occurrence (HR = 1.05; 95% CI 1.02 to 1.08, p = 0.0008). In contrast, being employed and being married were associated with a longer time-to-seizure occurrence (HR = 0.39 and 0.52; 95% CI 0.17 to 0.88 and 0.28 to 0.99, p = 0.0238 and 0.0466, respectively).

Clinical features: As noted in table 2, disease activity whether at TD, T0, TL or over time (HR = 1.11 to 1.24; 95% CI 1.07 to 1.19 to 1.15 to 1.29; p<0.0001), damage accrual at T0 (HR = 1.47; 95% CI 1.23 to 1.76; p<0.0001) but not at TL, psychosis (HR = 3.85; 95% CI 1.20 to 6.80; p = 0.0181), diffuse proliferative glomerulonephritis (HR = 4.18; 95% CI 2.16 to 8.09; p<0.0001), renal damage (HR = 2.22; 95% CI 1.12 to 4.38; p = 0.0214), aPL antibodies (HR = 2.87; 95% CI 1.26 to 6.52; p = 0.0120), the average dose of glucocorticoids (HR = 1.03; 95% CI 1.01 to 1.05; p<0.0001) and the use of cyclophosphamide (HR = 2.54; 95% CI 1.36 to 4.74; p = 0.0034) were associated with a shorter time-to-seizure occurrence whereas disease duration (HR = 0.18; 95% CI 0.11 to 0.29; p<0.0001), the presence of integument (HR = 0.20; 95% CI 0.11 to 0.38; p<0.0001) and musculoskeletal manifestations (HR = 0.09; 95% CI 0.04 to 0.21; p<0.0001) and the use of hydroxychloroquine (HR = 0.18; 95% CI 0.01 to 0.34; p<0.0001) were associated with a longer time-to-seizure occurrence.

Multivariable analyses—As noted in table 3, baseline disease activity and younger age were associated with a shorter time-to-seizure occurrence (HR = 1.01 and 1.04; 95% CI 1.04 to 1.15 and 1.00 to 1.08, p = 0.0004 and 0.0304), whereas the presence of mucocutaneous manifestations (HR = 0.34; 95% CI 0.16 to 0.41; p = 0.0039) and the use of hydroxychloroquine (HR = 0.35; 95% CI 0.15 to 0.80; p = 0.0131) were associated with a longer time-to-seizure occurrence.

Seizures and damage accrual—As noted in table 4, when seizures were examined in the context of other variables known to be associated with the accrual of damage (age, gender, ethnicity, poverty, disease duration, disease activity, glucocorticoid use),[1 18 19] seizures were Found to be an independent contributor to this outcome (χ^2 51.43, p<0.0001). As noted in table 5, the domains of the SDI most frequently associated with seizure occurrence were neuropsychiatric (seizures excluded), renal, musculoskeletal, gonadal and diabetes. As noted in table 6, however, only items from the renal (≥50% decreased glomerular filtration rate, proteinuria and end-stage renal disease) and neuropsychiatric (stroke) domains were significantly associated with seizures.

Seizures and mortality—When seizures were examined along with other variables known to independently affect survival and mortality in patients with SLE (age, gender, ethnicity, poverty, damage accrual), seizures were not found to have an independent effect on this outcome (data not shown).

DISCUSSION

Seizures are one of the most serious neuropsychiatric manifestations of SLE. They can occur at any time in the course of SLE and even before the diagnosis of lupus has been made or other manifestations of the disease are present.[20] In fact, up to 11% of neuropsychiatric manifestations of SLE occur before the disease is diagnosed.[20]21 In nine of our patients seizures occurred before the diagnosis of SLE have been made; in three of these nine patients, they occurred so many years before any manifestation of lupus ensued that attributing them to lupus is nearly impossible. Seizures are generally well controlled with the use of anticonvulsants but their occurrence is, unfortunately, a marker of damage accrual as demonstrated in the analyses presented; therefore, they portend a negative impact on the overall long-term prognosis and quality of life of patients with SLE on whom they occur. We have now examined the factors associated with time-to-seizure occurrence and have found African-American ethnicity, younger age, disease activity levels throughout the course of the disease, damage early in the course of the disease, psychosis, renal involvement, particularly WHO Class IV glomerulonephritis and renal damage at baseline, aPL antibodies, and glucocorticoid and cyclophosphamide use to be associated with a shorter time to their occurrence; in contrast, musculoskeletal and integument involvement and hydroxychloroquine use were associated with a longer time-to-seizure occurrence. Because TD is the starting point in all time-dependent analyses, the six patients in whom seizures occurred within a relatively short time from TD (3.5 years) could not be included as this will have required adding 3.5 years of disease duration to the other 40 patients. Moreover, variables that occurred after the event (medications, for example) could not be included in these analyses.

In the multivariable analysis younger age, disease activity (at baseline), mucocutaneous manifestations and hydroxychloroquine use, remained significant. As medication use was examined before the occurrence of seizures, our findings indicate that hydroxychloroquine may actually protect patients with SLE from developing them although the exact mechanism of how this protection occurs is not known; given the multiple possible mechanisms by which seizures may occur in patients with SLE, it is conceivable that the protective effect of hydroxychloroquine may result from a combination of its anti-inflammatory, antithrombotic and antiplatelet properties.[22]23 These data have obvious therapeutic implications for the management of patients with lupus and add to the numerous described benefits of this drug in patient with lupus.[24-29]

Higher levels of disease activity throughout the course of the disease were associated with a shorter time-to-seizure occurrence in our patients, even after removing them from the SLAM-R score; the association of the use of cyclophosphamide and glucocorticoids with a shorter time-to-seizure occurrence may be indicative of higher levels of disease activity beyond the baseline visit. Thus, disease activity is a risk factor for the occurrence of seizures but seizures also represent a marker of disease activity and severity in SLE. These data are in agreement with those reported by several other investigators around the world over the years.[30-34]

The aetiology of seizures is considered multifactorial; aPL antibodies (IgM/IgG) and lupus anticoagulant have been described to convey an increased risk of neurological and thrombotic disorders whether or not secondary to SLE.[35–37] In addition to inducing a prothrombotic state, it has been suggested that these antibodies may play an important role in the pathogenesis of seizures by non-ischaemic mechanisms, such as an increased neuronal excitability through

inhibition of γ-aminobutiric acid receptor-ion channel complex[38] or by binding to neuronal cell membranes, causing permeabilisation and depolarisation of brain synaptoneurosomes.[39] Furthermore, a vasculopathy characterised by arterial stenotic lesions has been described in patients with the aPL syndrome.[40] In our study, major thrombotic events of venous or arterial origin were not associated with a shorter time-to-seizure occurrence. aPL antibodies, on the other hand, were associated with a shorter time-to-seizure occurrence in the univariable analyses; however, this variable was not retained in the multivariable analyses. Given that these antibodies were not necessarily examined close to the event (seizures), and that their titres may vary with disease activity, they may still play an important role in their occurrence. Furthermore, antibodies against β_2-glycoprotein I (β_2-GPI), which are closely associated with thrombotic events in patients with SLE and the aPL syndrome and which may be present in the absence of other aPL antibodies, were not measured in our patients.[41,42]

Psychosis, renal involvement, particularly WHO Class IV glomerulonephritis and renal damage (per the renal domain of the SDI) were associated with a shorter time-to-seizure occurrence in the univariable analyses, whereas integument and musculoskeletal manifestations reflecting a less serious disease were associated with a longer time to their occurrence; however, only mucocutaneous manifestations remained in the multivariable model. Some of these manifestations, renal involvement in particular, may still be important contributing factors in some patients as it has been reported by other investigators.[34,43] Indeed, recent data on the understanding of chronic renal disease and its overall systemic consequences suggest that erythropoietin, which secretion is impaired in this setting, is important for neovascularisation,[44] impaired neovascularisation or impaired endothelial repair might lead to thrombotic or microthrombotic events in the central nervous system and be the basis for seizures to occur. The association of psychosis with a shorter time-to-seizure occurrence suggests that central nervous system involvement in SLE may be diverse and that purely psychopathological syndromes may occur in patients with defined structural abnormalities.[30]

In terms of the importance of seizures as indicative of worse things to come, we have shown that over and above other patients' characteristics known to be associated with the accrual of damage such as age, gender, disease activity, glucocorticoid use and disease duration,[1,18,19] the occurrence of seizures is an important contributor to the accrual of damage; these data underscore the importance of this clinical event in the lupus patient. In terms of the type of damage associated with the occurrence of seizures, they were in the neuropsychiatric, renal, musculoskeletal, diabetes and gonadal domains of the SDI. Within these domains, all items in the renal domain and stroke in the neuropsychiatric domain were found to occur more frequently in patients who had seizures than in those who did not. These data again emphasise the fact that seizures constitute a marker of other serious and even irreversible clinical events.

Seizures were not found to be independent contributors to mortality when examined in conjunction with variables known to be associated with this outcome. This finding should not be interpreted as indicative of their lack of impact on this distal clinical outcome given that they probably exert their influence through damage, a well recognised predictor of mortality.[18,45]

Our study is not without limitations. First, as already noted, we could not include patients whose seizures occurred prior to SLE diagnosis in the time-dependent analyses, even if due to lupus. Secondly, we have only examined the development of seizures at or after SLE diagnosis but not if they were recurrent or isolated events and the contributing factors to either course. Thirdly, we have not examined antineuronal or other antibodies in our cohort; thus, we do not know if they were associated with the occurrence of seizures. Fourthly, specific seizure biomarkers and whether they may differ by ethnic group were not determined. Finally, brain imaging studies such as magnetic resonance or computerised tomography were not necessarily

obtained to determine the presence or the extension of brain damage in those patients experiencing seizures as they were not required elements of the LUMINA study.

In summary, the present study provides important information for clinicians involved in the care of patients with lupus. First, although seizures tend to occur early in the course of the disease they may occur years later; conversely, they may herald the onset of lupus as they can occur years before the disease is diagnosed.[20] Secondly, seizures usually occur in the context of important disease activity and other serious clinical manifestations and in younger individuals. Thirdly, seizures are important determinants of damage accrual particularly occurring in the renal, neuropsychiatric, musculoskeletal, diabetes and gonadal domains of the damage index and as such they exert intermediate (and even long-term) impact or the course of SLE. Finally, and quite important, patients may be protected from their occurrence with the use of hydroxychloroquine.

Acknowledgements

The authors would like to acknowledge all patients in the LUMINA cohort without whom this study would have not been possible, our supporting staff (Martha L Sanchez, MD, MPH, Jie Zhang, MPH and Ellen D Sowell, AA at UAB. Cermine Pinilla-Diaz, MT at UPR and Robert Sandoval BA at UTH) for their efforts in securing our patients' follow-up and performing other LUMINA-related tasks and Ms Maria Tyson, AA for her expert assistance in the preparation of this manuscript. We also gratefully acknowledge Drs Robin Brey and John Hanly for their most helpful comments to an earlier version of this manuscript.

Funding: Supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases R01-AR42503 and P01 AR49084, General Clinical Research Centers M01-RR02558 (UTH) and M01-RR00032 (UAB) and from the National Center for Research Resources (NCRR/NIH) RCMI Clinical Research Infrastructure Initiative (RCRII) 1P20RR11126 (UPR); and fellowships from Rheuminations, Inc. and the STELLAR (Supporting Training Efforts in Lupus for Latino American Rheumatologists) program funded by Rheuminations, Inc. (UAB).

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Table 1

Univariable Cox regression analyses of baseline socio-economic—demographic variables and time-to-seizure occurrence in patients in the LUMINA cohort

Variable	HR (95% CI)	p Value
Younger age, years	1.05 (1.02 to 1.08)	0.0008
Gender, female	0.51 (0.23 to 1.15)	0.1043
Ethnicity		
Hispanic-Texan	4.12 (0.89 to 19.12)	0.0736
Hispanic-Puerto Rican	Reference group	
African American	5.37 (1.26 to 22.87)	0.0231
Caucasian	2.05 (0.43 to 9.90)	0.3708
Education, years	0.95 (0.86 to 1.04)	0.2491
Health insurance	0.61 (0.30 to 1.23)	0.1656
Employment	0.39 (0.17 to 0.88)	0.0238
Marital status	0.52 (0.28 to 0.99)	0.0466
Poverty level*	1.05 (0.53 to 2.10)	0.8915
Smoking	0.75 (0.27 to 2.12)	0.5889
Drinking	1.26 (0.39 to 4.09)	0.7013
Not exercising	0.92 (0.48 to 1.75)	0.7991

LUMINA, LUpus in MInorities: NAture versus Nurture.

*As per US Federal government guidelines.

Table 2

Univariable Cox regression analyses of clinical variables and time-to-seizure occurrence in patients in the LUMINA cohort

Variable	HR (95% CI)	p Value
Disease duration	0.18 (0.11 to 0.29)	<0.0001
SLAM-R score		
TD*	1.11 (1.07 to 1.15)	<0.0001
T0†	1.11 (1.07 to 1.16)	<0.0001
TL‡	1.15 (1.11 to 1.20)	<0.0001
Average	1.24 (1.19 to 1.29)	<0.0001
Average weighted	1.16 (1.11 to 1.22)	<0.0001
SDI score		
T0	1.47 (1.23 to 1.76)	<0.0001
TL	1.05 (0.91 to 1.21)	0.4820
Disease manifestations		
Integument	0.20 (0.11 to 0.38)	<0.0001
Musculoskeletal	0.09 (0.04 to 0.21)	<0.0001
Cardiovascular		
Hypertension	1.44 (0.77 to 2.70)	0.2521
Venous thrombosis	1.76 (0.74 to 4.20)	0.1763
Arterial thrombosis	1.13 (0.44 to 2.89)	0.7974
Neurological		
Stroke	2.02 (0.79 to 5.15)	0.1423
Psychosis	3.85 (1.20 to 6.80)	0.0181
Haematological	0.74 (0.29 to 1.88)	0.5200
Renal involvement	2.06 (1.02 to 4.14)	0.0426
WHO Class IV glomerulonephritis	4.18 (2.16 to 8.09)	<0.0001
Renal damage	2.22 (1.12 to 4.38)	0.0214
Auto-antibodies		
Anti-DNA	1.59 (0.83 to 3.04)	0.1647
Anti phospholipid§	2.87 (1.26 to 6.52)	0.0120
Medications		
Hydroxychloroquine	0.18 (0.01 to 0.34)	<0.0001
Glucocorticoid		
Average dose	1.03 (1.01 to 1.05)	<0.0001
Weighted average dose	1.00 (1.00 to 1.00)	0.3603
Cyclophasphamide	2.54 (1.36 to 4.74)	0.0034

LUMINA, LUpus in MInorities: NAture versus Nurture; SLAM-R, Systemic Lupus Activity Measure-Revised; SDI, SLICC (Systemic Lupus International Collaborating Clinics) Damage Index.

* Diagnosis time.

† Baseline.

[≠] Last visit.

[§] IgM, IgG and/or the lupus anticoagulant.

Table 3

Time-to-seizure occurrence by multivariable proportional hazard regression analysis in patients in the LUMINA cohort*

Variable	HR (95% CI)	p Value
Younger age, years	1.04 (1.00 to 1.08)	0.0304
SLAM-R†	1.10 (1.04 to 1.15)	0.0004
Mucocutaneous manifestations	0.34 (0.16 to 0.41)	0.0039
Hydroxychloroquine use	0.35 (0.15 to 0.80)	0.0131

LUMINA, LUpus in MInorities: NAture versus Nurture.

For alternative analyses, please refer to text.

*Adjusted for gender, ethnicity, marital status, disease duration, damage accrual (seizures excluded), disease manifestations (musculoskeletal, psychosis and renal damage) and medications (cyclophosphamide, average dose of glucocorticoids).

†Systemic Lupus Activity Measure-Revised at baseline (secures excluded).

Table 4

Poisson multivariable regression of damage accrual in patients in the LUMINA cohort

Variables	χ^2	p Value
Age, years	68.49	<0.0001
Gender, male	3.99	0.0459
Ethnicity		
Hispanic-Texan	35.22	<0.000l
Hispanic-Puerto Rican	Reference group	
African American	40.99	<0.000l
Caucasian	23.62	<0.000l
Poverty level	19.53	<0.0001
Disease duration, years	24.75	<0.0001
SLAM-R, average weighted score	170.30	<0.0001
Seizures	51.43	<0.0001
Glucocorticoid use, weighted average dose	20.78	<0.0001

LUMINA, LUpus in MInorities: NAture versus Nurture; SLAM-R, Systemic Lupus Activity Measure-Revised.

Table 5

Frequency distribution of the domains of the SLICC Damage Index as a function of seizure occurrence in patients in the LUMINA cohort

Damage domain, %	Seizures		p Value*
	Yes n = 40	No n = 559	
Ocular	22.5	15.2	
Neuropsychiatric†	42.5	25.4	0.0180
Renal	55.0	16.5	<0.0001
Pulmonary	5.0	7.3	
Cardiac	12.5	8.8	
Vascular	5.0	5.4	
Gastrointestinal	7.5	4.8	
Musculoskeletal	27.5	11.6	0.0036
Integument	12.5	15.4	
Gonadal	20.0	5.9	0.0006
Diabetes	17.5	6.4	0.0089
Malignancy	2.5	1.4	

SLICC, Systemic Lupus International Collaborating Clinics; LUMINA, LUpus in MInorities; NAture versus Nurture.

*Only values $p \leq 0.05$ are shown.

†Seizures excluded.

Table 6

Frequency distribution of items of selected domains of the SLICC Damage Index as a function of seizure occurrence in patients in the LUMINA cohort

Damage domains and items, %	Seizures		p Value*
	Yes n = 40	No n = 559	
Renal			
Decreased glomerular filtration rate (<50%) (n = 51)	32.5	6.8	<0.0001
Significant proteinuria (n = 85)	37.5	12.5	<0.0001
End-stage renal disease (n = 32)	30.0	3.4	<0.0001
Neuropsychiatric			
Cognitive impairment (n= 126)	30.0	20.2	
Stroke (n = 43)	25.0	5.9	<0.0001
Cranial or peripheral neuropathy (n = 22)	7.5	3.2	
Musculoskeletal			
Muscle atrophy (n = 18)	5.0	2.9	
Deforming arthritis (n = 22)	5.0	3.6	
Osteoporosis (n = 20)	7.5	3.0	
Osteonecrosis (n = 27)	10.0	3.4	0.0591
Osteomyelitis (n = 8)	0	1.4	

SLICC, Systemic Lupus International Collaborating Clinics; LUMINA, LUpus in MInorities NAture versus Nurture.

* Only p values ≤0.05 are shown.