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Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort

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Objective. Damage accrual in SLE has been previously shown to be an independent predictor of mortality. We sought to discern which SLICC Damage Index (SDI) domains are the most important predictors of survival in SLE.

Methods. SLE patients (ACR criteria), age $\geqslant$16 years, disease duration $\leqslant$5 years at enrolment, of African–American, Hispanic or Caucasian ethnicity were studied. Disease activity was assessed using the SLAM-Revised (SLAM-R) at diagnosis. Damage was ascertained using the SDI at the last visit. The SDI domains associated with time to death (and interaction terms) were examined by univariable and multivariable Cox proportional hazards regression analyses; those significant in the multivariable analyses were added to the final two models (with and without poverty) that included other variables known to be associated with shorter survival.

Results. A total of 635 SLE patients were studied of whom 97 (15.3%) have died over a mean (S.D.) total disease duration of 5.7 (3.7) years. Patients were predominantly women [570 (89.8%)]; their mean (S.D.) age was 36.5 (12.6) years; 126 (19.8%) had developed renal damage, 62 (9.3%) cardiovascular, 48 (7.8%) pulmonary and 34 (5.4%) peripheral vascular damage. When excluding poverty from the multivariable model, the renal domain of the SDI was independently associated with a shorter time to death (hazard ratio = 1.65; 95% CI 1.03, 2.66).

Conclusions. The renal domain of the damage index is associated with a shorter time to death when poverty, a strong predictor of this outcome, is removed from the model. Preventing renal damage in lupus patients has long-term prognostic implications.

Key words: Lupus, Renal damage, Mortality, Survival, Cohort, Ethnicity, SLICC damage index.

Introduction

SLE is a chronic multisystemic autoimmune disease with pleiotropic manifestations and a variable clinical course. At one end of the spectrum are the milder cases; at the other, the severe ones with multi-organ failure and early death. Although over the last two decades the 15-year probability of survival has improved significantly [1], the overall mortality in lupus patients is still higher than in the general population [2]. Moreover, higher mortality rates are found in non-white populations [3–5], and are, for the most part, explained by their less favourable socioeconomic status [3, 5, 6].

Over the last decade, we and others have consistently shown that low socioeconomic status, disease activity and overall damage as measured by SLICC Damage Index (SDI) are the most important predictors of poor survival in patients with SLE [4, 5, 7–10]. However, to our knowledge, the impact of the different domains of the damage index on survival has been examined only in one study and in a limited manner (univariable analyses) [11].

In the present study, we sought to discern which domains of the damage index are the most important predictors of survival in patients with SLE after taking into consideration other variables known to be associated with a diminished survival in these patients.

Patients and methods

Patients

LUMINA is a longitudinal outcome study of SLE patients of defined ethnicity (Hispanic, African–American, Caucasian) recruited at tertiary centres in Alabama, Texas and Puerto Rico; these patients meet the ACR criteria [12, 13], are $\geqslant$16 years of age and have a disease duration of $\leqslant$5 years at enrolment (T0). Each patient has a T0 visit during which medical records are reviewed to establish the time of diagnosis (TD). Follow-up visits are conducted every 6 months for the first year (T0.5 and T1, respectively), and yearly thereafter. During each visit a medical interview and a physical examination are performed and laboratory tests are obtained.

Approval from the Institutional Review Board for the Protection of Human Subjects was obtained at each centre. A written, signed informed consent was obtained from all patients.

Variables

The socioeconomic–demographic domain variables included were age, gender, ethnicity, poverty (as defined by the US Federal Government adjusted for the number of subjects in the household). Disease activity was assessed using the SLAM-Revised (SLAM-R) [13, 14] at TD. Damage was ascertained using the SDI [15] at the last visit (TL). In terms of the renal domain, and as per the instructions accompanying the instrument, a maximum of three points can be assigned to this domain. Thus, a patient who rapidly develops end-stage renal disease (ESRD) may paradoxically appear to have never had proteinuria or a diminished glomerular filtration rate (GFR), since all points are given to ESRD.

Statistical analyses

The analyses were conducted in two steps. In the first step, the domains of the SDI associated with a diminished probability of survival were examined in univariable and multivariable Cox regressions. In a second step, those domains of the SDI

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with a *P*-value <0.10 in this multivariable Cox regression were entered into multivariable Cox proportional hazards regression models in which variables previously shown to be associated with mortality in our cohort (age, gender, ethnicity, poverty and SLAM-R [6, 16]) were also included. Two models were examined: in the first model, poverty was included, while in the second it was excluded, so that other variables associated with the end point could be identified. Results are presented as hazard ratios (HRs) with their corresponding 95% CIs. HRs >1 indicate a shorter time to the event (death) or a decreased probability of survival while values <1 indicate a longer time or an increased probability of survival. Statistical significance was defined as a *P*-value $\leqslant 0.05$. Finally, adjusted survival estimates obtained from these Cox regression models were plotted as survival curves. TD was the starting point in these analyses.

Analyses were performed using either SAS, version 9.1 (SAS Institute, Cary, NC, USA) or SPSS, version 15.0 (SPSS, Chicago, IL, USA).

Results

Six hundred and thirty-five lupus patients constituted the LUMINA cohort at the time this study was conducted; of them 97 (15.3%) died over a mean (S.D.) total disease duration of 5.7 (3.7) years. The patients were predominantly women (89.8%) with a mean age (S.D.) of 36.5 (12.6) years. Among these patients 126 (19.8%) developed renal damage, 62 (9.3%) cardiovascular damage, 48 (7.8%) pulmonary damage and 34 (5.4%) peripheral vascular damage. Among those patients who developed renal damage, 56 (44.4%) had developed a $\geqslant 50\%$ decrease in GFR, 93 (78.8%) proteinuria, 38 (30.2%) ESRD; diminished GFR alone had occurred in 18 patients (14.3%) and proteinuria alone in 55 (43.7%); ESRD (rapidly progressing) was recorded in 10 (7.9%). The remaining 43 patients exhibited a combination of two or all of these features: 15 (11.9%) diminished GFR and proteinuria, 5 (4.0%) diminished GFR preceding ESRD, 5 (4.0%) proteinuria and ESRD apparently not preceded by a diminished GFR and 18 (14.3%) all three.

Step 1: selection of the domains of the damage index

The results of the univariable and multivariable analyses are shown in Table 1. The following domains of the SDI were found to be associated with mortality in the univariable analyses: renal, cardiovascular, pulmonary and peripheral vascular. However, only the renal and cardiovascular domains were significant in the multivariable analyses. Of note, interaction terms for the domains of the SDI significant in the univariable analyses were not significant in the multivariable analyses.

Step 2: multivariable analyses of mortality

The results of the multivariable analyses are shown in Table 2. In the first model, age (HR = 1.02; 95% CI 1.01, 1.05), disease activity at TD (HR = 1.04; 95% CI 1.02, 1.08) and

TABLE 1. Selection of the SLICC Damage Index[a] domains associated with a shorter time to death by univariable and multivariable cox regression analyses in LUMINA[b] patients

	Univariable			Multivariable		
Damage domain variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Ocular	1.29	0.83, 2.02	0.2647	–	–	–
Neurological	1.40	0.93, 2.10	0.1089	–	–	–
Renal[c]	2.02	1.34, 3.06	0.0008	1.80	1.07, 3.01	0.0269
Pulmonary	1.68	0.98, 2.86	0.0590	1.35	0.77, 2.38	0.2941
Cardiovascular (CV)[c]	2.36	1.49, 3.73	0.0003	1.91	0.93, 3.90	0.0776
Peripheral vascular (PV)[c]	2.76	1.47, 5.20	0.0016	0.61	0.08, 4.43	0.6244
Gastrointestinal	0.99	0.48, 2.05	0.9795	–	–	–
Musculoskeletal	1.23	0.76, 1.99	0.3923	–	–	–
Integument	1.43	0.89, 2.30	0.1436	–	–	–
Premature gonadal failure	0.94	0.51, 1.73	0.8427	–	–	–
Diabetes mellitus	1.29	0.67, 2.49	0.4482	–	–	–
Malignancy	0.74	0.18, 2.99	0.6694	–	–	–
Renal–CV[c]	–	–	–	0.79	0.27, 2.28	0.6640
CV–PV[c]	–	–	–	4.40	0.43, 44.78	0.2103
PV–Renal[c]	–	–	–	6.50	0.63, 66.84	0.1155
PV–Renal–CV[c]	–	–	–	3.06	0.26, 36.02	0.7900

[a]Systemic Lupus International Collaborating Clinics. [b]Lupus in Minorities: nature *vs* nurture; diagnosis was the starting point in these analyses. [c]Interaction terms between clinically related significant domains included.

TABLE 2. Variables independently associated with time to death by multivariable Cox proportional hazards regression analyses in LUMINA[a] patients

	Model 1			Model 2	
Variable	HR	95% CI		HR	95% CI
Age, years	1.02	1.01, 1.05		1.02	1.01, 1.04
Gender, male	0.52	0.28, 0.97		0.60	0.33, 1.07
Ethnicity					
Texan–Hispanic	2.26	0.64, 7.85		3.00	0.86, 10.21
Puerto Rican–Hispanic			Reference group		
African–American	2.47	0.73, 8.32		3.21	0.97, 10.66
Caucasian	1.76	0.50, 6.18		1.69	0.49, 5.83
Poverty	1.99	1.24, 3.18		–	–
SLAM-R	1.04	1.02, 1.08		1.04	1.01, 1.07
SDI					
Renal damage	1.19	0.97, 1.47		1.65	1.03, 2.66
Cardiovascular damage	1.51	0.91, 2.52		1.55	0.94, 2.56

[a]Lupus in Minorities: nature *vs* nurture; diagnosis was the starting point in these analyses.

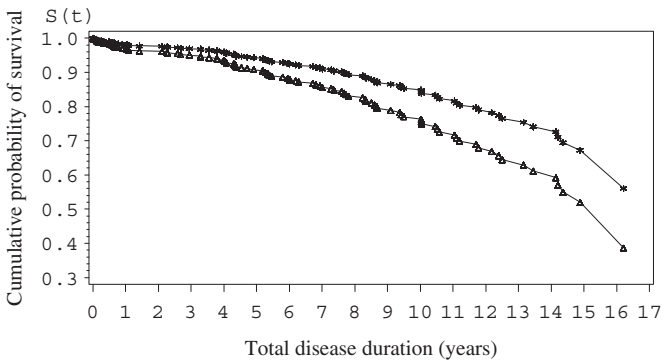

FIG. 1. Survival curves derived from the Cox proportional regression analysis (Model 2) adjusted for age, gender, ethnicity, disease activity at diagnosis and cardiovascular damage. *Renal damage absent and △renal damage present. The starting point in this graph is the date of diagnosis.

poverty (HR = 1.99; 95% CI 1.24, 3.18) were found to be significantly associated with a shorter time to death, whereas in the second model, the renal domain of the SDI was independently associated with a shorter time to death (HR = 1.65; 95% CI 1.03, 2.66). In contrast, although the HR was above the unit for the cardiovascular domain, the 95% CI encompassed the unit, and thus this association was not statistically significant. Survival curves as a function of renal damage derived from the second Cox proportional hazards regression model adjusted for age, gender, ethnicity, disease activity at baseline and cardiovascular damage are depicted in Fig. 1.

Discussion

We and others have previously shown that damage accrual in SLE is an independent predictor of mortality [5, 7–10] but which of the domains of the damage index is/are more important determinants of such association has not been examined in conjunction with other features known to affect the probability of survival in these patients. For example, Stoll *et al*. [11] have shown that the damage index score in the pulmonary domain was significantly higher in patients who succumbed to the disease at 1, 5 and 10 years but statistical significance was only achieved at 1 and 10 years; in these analyses, however, no adjustment for other possible confounders was performed. Although pulmonary damage was of borderline statistical significance in our univariable analyses, it was not significant subsequently and thus it was not entered into our final Cox model. We have now conducted such a study utilizing the data from LUMINA, a multiethnic cohort; from the four possible domains initially identified (pulmonary, peripheral vascular, renal and cardiovascular), two were entered into the multivariable Cox model: renal and cardiovascular. Of them, renal became significant, whereas, cardiovascular did not; significance, however, was only achieved when poverty was omitted from the model, underscoring again the importance of the socioeconomic factors as predictors of poor outcomes in patients with SLE as we and others have noted [3–5]. In this context, poverty which is highly associated with other socioeconomic parameters like (education, insurance, marital status and access to care) measures them as well [6, 10].

Renal involvement in SLE has been recognized as potentially leading to renal damage and even death [6]. Data from previous studies demonstrate that remission of active lupus nephritis is an important predictor of a favourable long-term outcome in these patients [17, 18]; moreover, in a recent study the 10-year patient survival was 95% for those patients with lupus nephritis who achieved complete remission, 76% for those achieving partial remission, but only 46% for those not attaining remission [18].

However, what is really surprising given the well-recognized occurrence of premature atherosclerosis in SLE patients is that when both the cardiovascular and the renal domains of the SDI were examined concomitantly the cardiovascular domain was not independently associated with a shorter time to death. A possible explanation could be that besides angina, myocardial infarction and congestive hearth failure, the cardiovascular domain of the SDI includes pericardial disease/pericardiectomy and valvular heart disease, which have a less ominous prognosis when compared with the three previously mentioned items of the cardiovascular domain. Second, it is possible that our data were not able to capture the cardiovascular items associated with premature atherosclerosis given the relatively young age of our patients as compared with that reported in other publications: our patients' mean age was 36 years, whereas it was 44 years in the Pittsburgh cohort [19] and 49 in the Toronto Lupus Cohort [20].

In summary, the renal domain of the damage index is associated with a shorter time to death when socioeconomic variables such as poverty are not taken into account but other variables known to affect this outcome are considered. This finding underscores the need to identify ways to prevent the accrual of renal damage in patients with SLE, not only by aggressively treating renal disease flares, but also by discovering better markers for disease activity as well as immunomodulatory therapies aimed at preventing the development of renal damage.

Rheumatology key messages

- The renal domain of damage index has an independent negative effect on survival in lupus.
- However, if poverty is included this effect becomes not significant, underscoring its importance on this outcome.

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