# RHEUMATOLOGY

## Concise report

# Disease features and outcomes in United States lupus patients of Hispanic origin and their Mestizo counterparts in Latin America: a commentary

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## Abstract

**Objective.** To evaluate disease features and outcomes in two populations with significant Amerindian ancestry.

**Methods.** Hispanic patients (from Texas) from the Lupus in Minorities: Nature versus Nurture (LUMINA) cohort and Mestizo patients from the Grupo Latino Americano De Estudio del Lupus or Latin American Group for the Study of Lupus (GLADEL) cohort were included. Disease features and outcomes were evaluated at baseline and last visit. Admixture informative markers of Mestizo Genoma de Lupus Eritematoso Sistémico Network consortium (GENLES) patients and Hispanic LUMINA patients were compared. Univariable analyses were performed using Chi square or Student's $t$ test as appropriate. Multivariable analyses adjusting for possible confounders were carried out using Poisson, logistic or Cox regression models as appropriate.

**Results.** A total of 114 LUMINA and 619 GLADEL patients were included. GLADEL patients had accrued more damage at baseline, but the opposite was the case at last visit. Being from LUMINA was a risk factor for damage accrual, even after adjusting for possible confounders [relative risk (RR) 1.33, 95% CI 1.12, 1.58]. Also, LUMINA patients have a higher risk of mortality than GLADEL patients [hazard ratio (HR) 2.37, 95% CI 1.10, 5.15], having 5-year survival of 85.6% and 94.5%, respectively. In addition, 79 LUMINA patients and 744 Mestizo GENLES patients were evaluated in order to compare genetic ancestry between the two groups; GENLES patients had a higher proportion of European ancestry (48.5% $vs$ 43.3%, P = 0.003) and a lower proportion of Asian ancestry (3.7% $vs$ 4.9%, P = 0.048), but the proportions of Amerindian and African ancestry were comparable in both.

**Conclusion.** USA Hispanic patients seemed to have a poorer prognosis than their counterparts from Latin America, despite having a comparable genetic background. Socioeconomic factors may account for these observations.

**Key words:** systemic lupus erythematosus, outcome, ethnic group, genetic predisposition to disease.

CLINICAL SCIENCE

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- Lupus patients with a large Amerindian ancestral background experience less favourable outcomes than Caucasian patients.
- Genetic ancestry and socioeconomic factors account for the poorer outcomes experienced by Amerindian lupus patients.

## Introduction

Hispanic ethnicity (defined in the USA as that of those individuals belonging or tracing their origins to a Spanish-speaking country) or being Mestizo (defined in Latin America as individuals with European and Amerindian ancestral background) has been shown to affect the course and outcome of lupus among SLE patients [1, 2]. Among Hispanic/Mestizo patients, regardless of where they are or originate from, those with a strong Amerindian ancestral background seem to fare worse than those with smaller proportions of these ancestral genes [3]; in fact, Amerindian ancestry is associated with an increased number of risk alleles for SLE [4]. However, Amerindian ancestry, in the USA and elsewhere, is associated not only with a higher number of risk alleles, but also with some socio-demographic characteristics that reflect their overall low socioeconomic status (SES), which also is known to impact on their prognosis [5, 6].

We have now attempted to evaluate the similarities and differences between patients from two well-established cohorts, both with a large number of patients with Amerindian background: the Lupus in Minorities: Nature versus Nurture (LUMINA) cohort and the Grupo Latino Americano De Estudio del Lupus or Latin American Group for the Study of Lupus (GLADEL) cohort. We will focus mainly on the socio-demographic and clinical features, and outcomes of these SLE patients. In addition, Mestizo patients from the Genoma de Lupus Eritematoso Sistémico Network consortium (GENLES) and LUMINA Hispanic patients were compared in order to evaluate their genetic ancestry.

## Methods

Both the LUMINA and GLADEL cohorts have been amply described in the literature [1, 5]. The LUMINA patients were recruited between 1994 and 2007 based on the updated 1997 ACR classification criteria [7] and include four ethnic groups (Caucasians, African-Americans, Hispanics from Texas and Hispanics from Puerto Rico), whereas those from GLADEL were recruited between 1997 and 2003 based on physician's diagnosis; most patients fulfilled the ACR criteria, although that was not a requisite. GLADEL includes three main ethnic groups (Caucasian, Mestizo and African–Latin American). The LUMINA study was approved by the institutional review boards of the participating institutions: The University of Alabama at Birmingham, The University of Texas–Houston Health Science Center, The University of Texas Medical Branch at Galveston and The University of Puerto Rico Medical Sciences Campus. The GLADEL cohort study was performed in accordance with the principles of the Declaration of Helsinki for the conduct of research in humans and following the regulations of local institutional review boards. The GENLES consortium was approved by the institutional review boards of all participating institutions, and the data used for the analyses had been obtained under these regulations, no additional ethical approval was necessary to conduct these secondary analyses. As we conducted secondary analysis of data generated in the LUMINA, GLADEL and GENLES studies, no additional ethical approval was deemed necessary.

For these analyses, Hispanic patients (from Texas) from the LUMINA cohort and Latin American Mestizo patients from the GLADEL cohort constitute the study population. Only patients who fulfilled four of the 1997 ACR criteria [7] were included. Diagnosis time was time to fourth criterion. Demographic and clinical data from these patients were extracted. SES was defined as being below the federally defined poverty line in LUMINA and as per the Graffar [8] method in GLADEL. Acute onset was defined as less than a month between the accrual of the first and fourth criteria. Renal disorder was defined as the presence of the renal ACR criterion. Disease activity was ascertained with the SLAM in the LUMINA patients and with the SLEDAI in the GLADEL cohort. Moderate to high disease activity was defined as a SLAM $>7$ or a SLEDAI $>4$. Disease damage was ascertained using the SLICC/ACR damage index (SDI). Data were obtained from the baseline or the last visit.

To evaluate whether Amerindian ancestry could explain the difference between these groups, data from GENLES and LUMINA were compared. Even though only a relatively small number of GLADEL patients were part of GENLES, nevertheless they were drawn from the same geographical area as those from GLADEL, and it is expected that they would have a similar ancestry to the GLADEL patients. A total of 347 admixture informative markers were used to genotype these patients, as has previously been reported [4].

### Statistical analyses

Baseline characteristics for the LUMINA and GLADEL patients were compared using Chi square or Student's *t*-test as appropriate. The number of ACR criteria accumulated during follow-up was examined using a Poisson regression model, adjusting for disease duration; for the last SDI, a Poisson regression model adjusting for age at diagnosis, disease duration and baseline SDI was performed (model 1); an alternative model adding disease activity at baseline (defined as remission to mild *vs* moderate to high) was also used (model 2). For the presence of any damage and renal damage at last visit, logistic regression models, adjusting for age at diagnosis, disease

duration and baseline SDI were run. Mortality rates among patients in the two cohorts were compared using univariable and multivariable Cox regression models, the latter adjusting for age at diagnosis, gender and the baseline SDI (model 1). An alternative model, also including other possible confounders such as SES (medium to high *vs* low) and disease activity at baseline (defined as remission to mild *vs* moderate to high) was also run (model 2). Comparison between LUMINA and GENLES ancestry markers was performed using Student's *t*-test. All statistical analyses were performed using SPSS v. 21.0 (Chicago, IL, USA).

## Results

A total of 114 LUMINA and 619 GLADEL patients were included in these analyses. Age and gender were similar in both groups; however, patients from LUMINA have longer disease duration. A low SES was most frequent among GLADEL patients, yet health insurance coverage was similar between the two groups. These data are presented in Table 1.

At baseline, GLADEL patients had a higher SDI. At their last visit, patients from LUMINA had a higher SDI; being from LUMINA remained a risk factor for damage accrual, even after adjusting for age, gender, disease duration and baseline SDI (model 1); the same was the case in the alternative model (model 2), which also included disease activity at baseline. However, the proportion of patients with at least one point in the SDI at last visit was comparable in both cohorts. These data are presented in Table 2. In the multivariable analysis, renal damage occurred with similar frequency in both cohorts (data not shown). The 5-year survival probabilities for the LUMINA and GLADEL patients was 84.6% and 94.5%, respectively. LUMINA patients have a higher risk of mortality than the GLADEL patients in both the univariable (HR = 2.45, 95% CI 1.39, 4.31; P = 0.002) and multivariable analyses, after adjusting for age at diagnosis, gender and the baseline SDI (HR = 2.74, 95% CI 1.53, 4.89; P = 0.001) (model 1). The alternative model (adjusting also for baseline disease activity and SES) showed similar results (model 2). These data are depicted in Table 2.

A total of 744 GENLES Mestizo patients and 79 LUMINA patients were included in this analysis. The proportion of African ancestral genes was comparable in the two patient groups (4.1% *vs* 5.0%; P = 0.327); there was a larger European component in the GENLES patients (48.5% *vs* 43.3%; P = 0.003), and smaller Asian (3.7% *vs* 4.9%; P = 0.048) and Amerindian (43.7% *vs* 46.9%; P = 0.088) components as compared with the LUMINA patients; the latter difference was not significant.

## Discussion

USA Hispanics and Latin American Mestizo patients share unfavourable short, intermediate and long-term outcomes [2]. These outcomes are probably related to the patients' genetic background, but are also influenced by their socio-demographic characteristics. Within these two groups, the USA Hispanics fared even less favourably than their Mestizo counterparts from Latin America. For example, despite comparable proportions of patients with acute disease onset, renal involvement and moderate to high disease activity, the Hispanic USA patients accrue more damage and experience a lower survival rate than their Latin American counterparts. In addition, the proportion of patients without damage was similar in both cohorts, but smaller than previously reported in other cohorts [9–12]. These data suggest that Amerindian ancestry is associated with rapid damage accrual, as previously described by Alarcón *et al*. [13].

The 5-year survival rate was lower than reported in other cohorts from the USA and Europe [14–17]; this was particularly the case for the LUMINA cohort patients. Although it is attractive to think that the explanation of the poorer prognosis of Hispanic USA patients lies in the combination of the patients' low SES (particularly the lack of adequate health insurance) [5, 18] and their high-risk genetic profile, other variables not yet identified may be of importance.

We and others have previously reported that the differences in the occurrence of organ system involvement (such as renal involvement) observed among SLE patients of different ethnic groups can be explained, at least in part, by genetic ancestral genes and/or environmental factors (like low SES or occupational exposures) [19]. Given this premise, we were interested in comparing the genetic ancestry of these two patient groups; although nearly 70% of LUMINA patients have been genotyped, that was not the case with the GLADEL patients. However, there were genetic data from patients studied by the GENLES consortium, which probably have a very similar genetic structure to those from GLADEL. Some differences were observed in the proportion of European (more in the GENLES patients) versus Amerindian (more in the LUMINA patients) ancestral genes, which could explain the less favourable outcomes in the LUMINA patients; we think, however, these differences are not large enough to be the sole cause of the differences observed.

These comments should not be taken out of context; rather, they should be interpreted with caution. First, some of the data are not directly comparable in the two cohorts. For example, low SES in the USA as measured by the federally defined poverty level is not equivalent to the Graffar scale; individual SES components other than health insurance (education, income, housing, social support, etc.) were not available in the GLADEL cohort; disease activity was measured using two different indices, which prevents these evaluations being exactly comparable. Other variables known to affect intermediate and long-term outcomes (such as environmental exposures, disease activity over time, the number of flares, and the use of detrimental and protective medications) could not be directly compared due to the differences between the two protocols. Second, some unmeasurable differences between the LUMINA and GLADEL patients may have an important impact on the course and outcome of lupus;

TABLE 1 Salient features of USA Hispanic SLE patients from LUMINA and Latin America Mestizo patients from GLADEL (at diagnosis or at last visit)

| Characteristic | LUMINA (n = 114) | GLADEL (n = 619) | P-value |
|---|---|---|---|
| Age, mean (S.D.) | 31.3 (12.2) | 29.4 (12.6) | 0.138 |
| Gender, female, n (%) | 106 (93.0) | 546 (88.2) | 0.135 |
| Disease duration, mean (S.D.) years | 6.1 (4.3) | 4.4 (2.3) | <0.001 |
| Low SES[a], n (%) | 42/107 (39.3) | 391 (63.2) | <0.001 |
| Health insurance, n (%) | 56/112 (50.0) | 328/615 (53.3) | 0.516 |
| Acute onset, n (%) | 34 (29.8) | 151 (24.4) | 0.220 |
| ACR criteria number[b], mean (S.D.) | 6.8 (1.6) | 6.3 (1.5) | 0.099 |
| Disease activity, moderate–high[c], n (%) | 78/92 (84.8) | 438/493 (88.8) | 0.268 |
| Renal disorder, n (%) | 60 (52.6) | 370 (59.8) | 0.155 |
| SDI at baseline, mean (S.D.) | 0.6 (1.1) | 1.0 (1.2) | 0.003 |
| SDI ⩾ 1 at baseline, n (%) | 41 (36.0) | 336 (54.3) | <0.001 |
| SDI score at last visit, mean (S.D.) | 2.3 (2.6) | 1.7 (1.7) | 0.025 |
| SDI ⩾ 1 at last visit, n (%) | 80 (70.2) | 446 (72.1) | 0.164 |
| Renal damage (per the SDI, at last visit), n (%) | 37 (32.5) | 184 (29.7) | 0.907 |
| Five-year survival, % | 84.6 | 94.5 | 0.002 |
| Deceased, n (%) | 21 (18.4) | 35 (5.7) | <0.001 |

[a]SES defined as being below the federally defined poverty line for LUMINA and as per the Graffar method for GLADEL. [b]After adjusting for disease duration using a Poisson regression model. [c]Defined as a SLAM >7 for LUMINA and a SLEDAI >4 for GLADEL. GLADEL: Grupo Latino Americano De Estudio del Lupus or Latin American Group for the Study of Lupus; LUMINA: Lupus in Minorities: Nature versus Nurture; SES: socioeconomic status; SDI: SLICC Damage Index.

TABLE 2 Damage accrual and mortality of USA Hispanic SLE patients from LUMINA and Latin America Mestizo patients from GLADEL (at last visit)

| Characteristic | Multivariable analyses[a] | P-value |
|---|---|---|
| SDI score at last visit, model 1, RR (95% CI)[b] | 1.33 (1.12, 1.57) | 0.001 |
| SDI score at last visit, model 2, RR (95% CI)[c] | 1.33 (1.12, 1.58) | 0.001 |
| SDI ⩾1 at last visit, OR (95% CI)[b] | 1.06 (0.56, 1.99) | 0.859 |
| Five-year mortality, model 1, HR (95% CI)[d] | 2.76 (1.54, 4.94) | 0.001 |
| Five-year mortality, model 2, HR (95% CI)[e] | 2.37 (1.10, 5.14) | 0.029 |

[a]Mestizo patients from GLADEL are the reference group. [b]After adjusting for age at diagnosis, gender, baseline SDI and disease duration. [c]After adjusting for age at diagnosis, gender, moderate–high disease activity at baseline, baseline SDI and disease duration. [d]After adjusting for age at diagnosis, gender, low socioeconomic status, moderate–high disease activity at baseline and baseline SDI. [e]After adjusting for age at diagnosis, gender, low socioeconomic status, moderate–high disease activity at baseline and baseline SDI. GLADEL: Grupo Latino Americano De Estudio del Lupus or Latin American Group for the Study of Lupus; LUMINA: Lupus in Minorities: Nature versus Nurture; SDI: SLICC Damage Index.

many of the LUMINA Hispanic patients are first-generation immigrants who have not been acculturated to mainstream culture and who have limited communication skills; they may, thus, have tremendous difficulties in accessing care compared with non-Hispanic patients of the same SES; it has been shown, for example, that area or neighbourhood poverty carry an additional toll in lupus patients, and that may apply to this poorly integrated patient group [20]. Third, the assumption made that the genetic ancestral background of the GLADEL patients studied is comparable to that of the larger GENLES consortium may not be exactly true. Despite these limitations, the comparisons presented herein have been performed on patients from two of the largest cohorts of Hispanic/

Mestizo SLE patients, and as such deserve some attention. Hispanic/Mestizo patients with a large Amerindian ancestral background, like those of African ancestry in the USA or the UK, seem to be at high risk of developing SLE and to experience poorer outcomes than Caucasian patients. However, further elucidation of the role of genetic ancestry and socioeconomic factors is needed.

## Acknowledgements

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