Commentary

International Journal of Clinical Rheumatology

What impact do race and ethnicity have on lupus mortality?

"Behavioral, psychosocial factors and co-morbidities (for instance, obesity) are highly correlated and participate as mediators of health outcomes as well as confounders."

Keywords: disparities • ethnicity • mortality • outcome • race • systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that affects predominantly women of childbearing age, with protean clinical manifestations involving virtually any organ including vital organs such as the heart, kidneys and CNS [1].

It is well recognized that some US minorities such as African–Americans, Hispanics and Asians have a worse disease course (e.g., a higher incidence of renal disease) [2]. These minorities have also been found to have a greater likelihood of progression to end stage renal disease (ESRD), and ultimately a higher damage accrual [3].

Several studies have also reported higher mortality rates (MRs) among non-Caucasian patients, with mortality rates two- to threefold higher among African–Americans [4–8]. The US Centers for Disease Control reported significant differences by age and race in MRs among SLE patients ≥15 years old, between 1979 and 1998. MRs were highest among African–Americans and patients >45 years old [9].

In a study conducted in South Carolina that included 6521 admitted SLE patients, Anderson and colleagues [7] reported that African–American patients had a 15% higher risk of mortality than white patients, after adjusting for health insurance, socioeconomic status, length of stay and co-morbidity index. The leading cause of death in African–American patients was SLE (20%). In a subgroup analysis, African–American patients younger than 50 years of age were less likely to die of malignancy than white patients, and more likely to die of infections.

Some, but not all studies, have reported higher MRs among residents in the USA of Asian descent [4]. Other studies conducted in Asian countries reported specific differences among Asian SLE patients based on their origin. For example, Wang demonstrated a reduced survival among Asian Indian patients compared with Chinese and Malay patients in Malaysia [10]. It is important to bear in mind that mortality studies in SLE are often difficult to compare since they are composed of different ethnic populations at various stages of disease.

Most of the studies conducted in US minorities share some limitations regarding the misclassification of Hispanic patients as a unique group, regardless of their origin. Asians patients are often misclassified as well, without distinguishing patients from the Middle East, Southeast or Pacific Islands.

Ethnicity is a complex sociological term that involves several factors including ancestral genes, regions of residence, socioeconomic and cultural factors. Thus, it is not a simple task to label a heterogeneous group such as Hispanics as a unique group that shares Spanish as their primary language as its main characteristic given the wide range of genetic, socioeconomic and biological differences [11].

For these reasons, a subgroup analysis is recommended in studies analyzing Hispanic populations. For example, the LUMINA study reported higher MRs among Texan Hispanics than in Puerto Rican Hispanics, but those differences disappear after adjusting socioeconomic status [12].

José A Gómez-Puerta
Author for correspondence:
Grupo de Inmunología Celular e Inmunogenética (GICIG), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia, and,
Sección de Reumatología, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
Tel.: +57 4218 6448
Fax: +54 4219 6450
jgomezpuerta@mail.harvard.edu

Gloria Vásquez
Grupo de Inmunología Celular e Inmunogenética (GICIG), Universidad de Antioquia, Colombia, and,
Sección de Reumatología, Universidad de Antioquia, Colombia

Future Medicine part of fsg

The GLADEL (Grupo LatinoAmericano De Estudio de Lupus, Latin American Group for the Study of Lupus) cohort is a well-defined group of more than 1200 Latin American patients with SLE from nine countries with a disease diagnosis of at least 2 years at entry [13]. When authors analyzed mortality among groups, there were no significant differences in survival rates between whites and non-whites (Mestizos and African–Latin Americans).

There is enough evidence that African–Americans have the worst prognosis among SLE patients, including more organ damage and higher mortality. However, data from Hispanic and Asian populations with SLE living in the USA are inconclusive. We recently reported two studies in patients with ESRD due to lupus nephritis (LN) [14] and in Medicaid population with SLE [15] and with some unexpected results. Hispanic and Asian patients had a better survival rate than their counterparts, despite a higher burden of cardiovascular risk factors. These unexpected results are discussed briefly in the current editorial.

Mortality in patients with ERSD due to lupus nephritis

It is well known that SLE patients who reach ESRD have a higher mortality risk. In addition, some differences between races and ethnicities have been described in patients with ESRD. Those differences can be explained in part by disparities in accessing healthcare among races/ethnicities. African–American patients are less likely to use peritoneal dialysis or preemptive transplant as initial renal replacement therapies [16], and have an increased risk of graft loss [17].

Recently, we reported a more favorable outcome in Hispanic and Asian patients in terms of cardiovascular events, and mortality in patients with ESRD due to LN [14]. We conducted a retrospective study using data from the US Renal Data System, the national registry of patients with ESRD. We were able to identify over 12,000 patients with ESRD with diagnosis of SLE as the main cause of ESRD from 1995 to 2008.

In crude analysis (unadjusted) and taking competing risk of kidney transplant and loss to follow-up into account, African–American and non-Hispanic LN ESRD patients had higher rates for all-cause mortality, compared with their counterparts (Asian and Hispanics).

In a fully adjusted model that adjusted for age and sex, age at ESRD onset, initial renal replacement modality, estimated glomerular filtration rate, multiple demographic factors and co-morbidities including smoking, hypertension, diabetes mellitus and coronary artery disease among others and also accounting for competing risks (kidney transplantation and loss to follow-up), Asians (vs whites) and Hispanics (vs non-Hispanics) with LN-associated ESRD patients had a 30 and 21% lower risk of mortality, respectively. Conversely, African–American patients experienced higher mortality with a 27% higher risk of death than white patients (95% CI: 1.18–1.36).

We also performed an age-stratified analysis, and differences according to race/ethnicity persisted. African–American LN-associated ESRD patients <40 years had an almost 70% higher risk of death than white patients. In the group between 40 and 59 years, African–American patients had a 26% higher risk than their white counterparts. Hispanic patients between 40 and 59 years and ≥ 60 years, had 22 and 24% respectively, lower adjusted mortality than non-Hispanics.

Other groups, reported recent similar results in patients with all-cause ESRD [18] and in patients with LN-associated ESRD [19]. Sexton and colleagues [19] reported that African–American and non-Hispanic patients had a higher mortality risk. Additionally, other factors related with worse prognosis were older age, smoking, diabetes and peripheral vascular disease. At the same time, differences in MRs by age were also recently reported in a large observational study that included patients with all-cause ESRD in the USA [20]. African–American patients ≤50 years had increased MRs compared with white patients.

Mortality in Medicaid recipients with SLE

Medicaid has become the main public health insurance program in the USA for the low-income population, covering over 62 million Americans. It is also the predominant source of coverage and financing of long-term care services for the elderly and individuals with disabilities. Medicaid covers one in five Americans and covers more than one in three children [21].

We analyzed data between the years 2000 and 2006 from the administrative Medicaid database, identifying 42,221 prevalent cases of SLE. Among the cases, 8191 had LN [15].

Co-morbidities included hypertension in 31%, diabetes in 24%, atherosclerosis in 16% and angina in 12%. The analysis adjusted for SLE-specific co-morbidities including pericarditis, thrombocytopenia, seizures and hemolytic anemia, using a risk adjustment index described by Ward [22].

During a mean follow-up of 2.6 years, there were 2058 deaths in the overall cohort, for an unadjusted mortality rate of 19.07 (95% CI: 18.36–19.91) per 1000 person-years. Among the subgroup with LN, there were 774 deaths, for a mortality rate of 44.64 (95% CI: 41.60–47.90) per 1000.

In a model that adjusted only for age and sex, Hispanic and Asian patients had MRs less than half than those of whites (hazard ratios: 0.41, 95% CI: 0.34–0.50 and 0.30, 95% CI: 0.21–0.43), while African–Americans and native Americans had higher rates (hazard ratios: 1.36, 95% CI: 1.24–1.49 and 1.43, 95% CI: 1.06–1.92).

The final model also adjusted for cardiovascular and lupus-related co-morbidities, and resulted in somewhat attenuated, though still significant, between-group differences. For instance, the 36% higher mortality risk among African–Americans decreased to 21% in the fully adjusted model.

Despite the fact that we had a relatively short follow-up (<3 years of average), we found a great disparity in MRs and adjusted hazard ratios among Medicaid recipients with SLE according to patients' race/ethnicity.

Conclusion & future perspective

The relationships of race/ethnicity to socioeconomic status, lifestyle factors and co-morbidities, all of which are related to SLE outcomes as well, are extremely complex. Behavioral, psychosocial factors and co-morbidities (for instance, obesity) are highly correlated and participate as mediators of health outcomes as well as confounders. It is difficult to draw definitive conclusions owing to difficulties in investigating mediation, the presence of unmeasured confounders and the likely bidirectional relationships between psychosocial, behavioral factors and co-morbidities over time.

Despite this complexity and interrelation, we described higher MRs among African–Americans, and lower MRs among Hispanics and Asians living in the USA in two different SLE populations (patients from Medicaid and patients with LN-related ESRD), reflecting the importance of race and ethnicity as critical independent factors for mortality in patients with SLE.

Further studies are needed in different populations in order to elucidate the specific weight of race/ethnicity over MRs. In addition, new studies evaluating ethnic subgroups are necessary with some other relevant clinical parameters such as disease activity and treatment.

Acknowledgement

JA Gómez-Puerta is enormously grateful to KH Costenbader for her contributions and critical review of the content of two main articles cited in the current editorial.

Financial & competing interest disclosure

JA Gómez-Puerta was supported by Colciencias (convocatoria 656 de 2014). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

References

1 D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. *Lancet* 369(9561), 587–596 (2007).

2 Ishimori ML, Gudsoorkar V, Venturupalli SR *et al.* Disparities in renal replacement in lupus nephritis: current practice and future implications. *Arthritis Care Res. (Hoboken)* 63(12), 1639–1641 (2011).

3 González LA, Toloza SM, McGwin G Jr, Alarcón GS. Ethnicity in systemic lupus erythematosus (SLE): its influence on susceptibility and outcomes. *Lupus* 22(12), 1214–1224 (2013).

4 Kaslow RA. High rate of death caused by systemic lupus erythematosus among U.S. residents of Asian descent. *Arthritis Rheum.* 25(4), 414–418 (1982).

5 Walsh SJ, Gilchrist A. Geographical clustering of mortality from systemic lupus erythematosus in the United States: contributions of poverty, Hispanic ethnicity and solar radiation. *Lupus* 15(10), 662–670 (2006).

6 Krishnan E, Hubert HB. Ethnicity and mortality from systemic lupus erythematosus in the US. *Ann. Rheum. Dis.* 65(11), 1500–1505 (2006).

7 Anderson E, Nietert PJ, Kamen DL, Gilkeson GS. Ethnic disparities among patients with systemic lupus erythematosus in South Carolina. *J. Rheumatol.* 35(5), 819–825 (2008).

8 Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: the Georgia Lupus Registry. *Arthritis Rheumatol.* 66(2), 357–368 (2014).

9 Sacks JJ, Helmick CG, Langmaid G *et al.* Centers for Disease Control, Prevention (CDC). Trends in deaths from systemic lupus erythematosus – United States, 1979–1998. *MMWR Morb. Mortal. Wkly Rep.* 51(17), 371–374 (2002).

10 Wang F, Wang CL, Tan CT, Manivasagar M. Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. *Lupus* 6(3), 248–253 (1997).

11 Pons-Estel GJ, Alarcón GS. Lupus in Hispanics: a matter of serious concern. *Cleve. Clin. J. Med.* 79(12), 824–834 (2012).

12 Fernandez M, Alarcón GS, Calvo-Alen J *et al.* A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum.* 57(4), 576–584 (2007).

13 Pons-Estel BA, Catoggio LJ, Cardiel MH *et al.* The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus

erythematosus: ethnic and disease heterogeneity among 'Hispanics'. *Medicine (Baltimore)* 83(1), 1–17 (2004).

14 Gómez-Puerta JA, Feldman CH, Alarcón GS, Guan H, Winkelmayer WC, Costenbader KH. Racial and ethnic differences in mortality and cardiovascular events among patients with end-stage renal disease due to lupus nephritis *Arthritis Care Res. (Hoboken)* doi: 10.1002/acr.22562 (2015) (Epub ahead of print).

15 Gómez-Puerta JA, Barbhaiya M, Guan H, Feldman CH, Alarcón GS, Costenbader KH. Racial/Ethnic variation in all-cause mortality among United States medicaid recipients with systemic lupus erythematosus: a Hispanic and asian paradox. *Arthritis Rheumatol.* 67(3), 752–760 (2015).

16 Devlin A, Waikar SS, Solomon DH *et al.* Variation in initial kidney replacement therapy for end-stage renal disease due to lupus nephritis in the United States. *Arthritis Care Res. (Hoboken).* 63(12), 1642–1653 (2011).

17 Nee R, Jindal RM, Little D *et al.* Racial differences and income disparities are associated with poor outcomes in kidney transplant recipients with lupus nephritis. *Transplantation* 95(12), 1471–1478 (2013).

18 Arce CM, Goldstein BA, Mitani AA, Winkelmayer WC. Trends in relative mortality between Hispanic and non-Hispanic whites initiating dialysis: a retrospective study of the US Renal Data System. *Am. J. Kidney Dis.* 62(2), 312–321(2013).

19 Sexton DJ, Reule S, Solid C, Chen SC, Collins AJ, Foley RN. ESRD from lupus nephritis in the United States, 1995–2010. *Clin. J. Am. Soc. Nephrol.* 10(2), 251–259 (2015).

20 Kucirka LM, Grams ME, Lessler J *et al.* Association of race and age with survival among patients undergoing dialysis. *JAMA* 306(6), 620–626 (2011).

21 Kaiser Family Foundation www.ktt.org

22 Ward MM. Development and testing of a systemic lupus-specific risk adjustment index for in-hospital mortality. *J. Rheumatol.* 27(6), 1408–1413 (2000).