Clinical Rheumatology (2019) 38:1865–1871
https://doi.org/10.1007/s10067-019-04546-w

ORIGINAL ARTICLE

Mortality in patients with systemic lupus erythematosus in Colombia: a case series

David Aguirre-Valencia[1,2] · Ana Suárez-Avellaneda[2] · Vanessa Ocampo-Piraquive[2] · Iván Posso-Osorio[1] · Juan Naranjo-Escobar[1] · Ivana Nieto-Aristizábal[1] · Gabriel J. Tobón[1,2,3] · Carlos A. Cañas[1,2]

Received: 23 November 2018 / Revised: 29 March 2019 / Accepted: 3 April 2019 / Published online: 15 April 2019

Abstract

Introduction Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with high mortality rates. This study aimed to describe the main causes of death in a case series of SLE patients attended in a single center in Colombia.

Methods We conducted a retrospective review and analysis of records of SLE patients who died between January 2011 and June 2017. We extracted the main causes of death and described variables associated with this outcome as well as variables associated with the disease and its treatment.

Results From a total of 1776 patients with SLE, we identified 49 fatal cases (89.8% women, $n = 44$). The average age at death was 40.6 years (SD 17.4), and patients had a median of 4.5 years (IQR 2–8) of disease duration. The main findings included lymphopenia in 44 patients (89.9%), biopsy-confirmed lupus nephritis (LN)—types IV and VI—in 38 (77.6%), catastrophic antiphospholipid syndrome (CAPS) in 8 (16.3%), and persistent hypocomplementemia (C3 and C4) in 8 (16.3%). The median SLE disease activity index (SLEDAI-2K) score at the time of death was 19 (IQR 11–39). The main cause of death was SLE activity and lupus-induced damage in 22 (44.9%) patients.

Conclusion The main causes of death included SLE activity refractory to immunosuppressive treatment, and nosocomial bacterial infections. The patients who died had persistently high SLEDAI scores, types IV and VI LN, associated antiphospholipid syndrome, and persistent hypocomplementemia, requiring severe immunosuppression and prolonged hospitalization.

Keywords Immunosuppression · Mortality · Outcomes · SLEDAI · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE), is a chronic autoimmune disease of unknown etiology, that has multi-organ involvement with variable relapse and remission periods. Some patients have persistently high active disease and organ involvement that leads to death despite conventional treatments. SLE patients have a 2–5 times higher mortality risk than the general population [1–3]. SLE mortality can be attributed to a myriad of interacting factors, including systemic involvement and complications associated with immunosuppressive treatment [3].

Patients' survival has improved over the years. In 1950, SLE patients' 5-year survival rate was 50%; between 1975 and 1990, it increased to 64–87%. Between 1990 and 2004, the 10-year survival rate was 78% [3, 4]. Currently, 5-year survival is estimated to be 96%, 10-year survival is 93%, and 15-year survival is 76%. However, some patients with rapidly progressive forms of the disease die in spite of adequate immunosuppressive treatment. For example, male patients with lupus nephritis (LN) have a higher mortality risk than females [5, 6]. A meta-analysis revealed that mortality secondary to kidney disease in SLE patients was 4.6 times higher than that of healthy controls, while the mortality secondary to cardiovascular disorders was 2.2

✉ Gabriel J. Tobón
gjtobon@icesi.edu.co

[1] GIRAT: Grupo de Investigación en Reumatología, Autoinmunidad y Medicina Traslacional, Fundación Valle del Lili and Universidad Icesi, Cali, Colombia

[2] Medical School, Universidad Icesi, Cali, Colombia

[3] Immunology Laboratory, Fundación Valle del Lili, Cra 98 No. 18-49, Cali, Colombia

times higher, and secondary to infections was 4.9 times higher than healthy individuals' mortality [7].

The Latin American Group for the Study on Lupus (*Grupo Latino Americano De Estudio del Lupus*, GLADEL) found that SLE disease activity is higher in black and Hispanic patients, and lower in white patients, according to the SLE disease activity index (SLEDAI) and the MEX-SLEDAI (index validated in Mexico). Other mortality predictors were formal education < 10 years, inadequate or no health insurance, age > 27 years at the time of diagnosis, delayed diagnosis for more than 6 months, and illness duration greater than 32 months [8]. Another index used as a mortality predictor is the SLICC-FI (Systemic Lupus International Collaborating Clinics—frailty index). Frailty is associated with a significant increase in the risk of mortality (log rank test $p < 0.0001$) and mortality is four times higher among frail individuals compared with non-frail patients [9].

The main final causes of death in SLE patients are chronic renal failure, cardiovascular disease, and infections. The first two causes are associated with disease progression, and the latter is associated with immunosuppressive treatment and immune system alterations inherent to SLE [3, 10].

The causes specifically related to SLE mortality in southwestern Colombia are unknown. The population in this region contains a mix of three ethnic groups: white, black, and indigenous peoples. A retrospective analysis of SLE mortality in a high-complexity medical center such as ours may identify variables in this population associated with fatal outcomes. Knowledge of these factors would help improve therapeutic strategies (including some that are currently experimental). As Albert Einstein noted, "Insanity is doing the same thing over and over again, but expecting different results." We tend to increase immunosuppression in patients with active and advanced disease, and in patients with reparative inflammation phase disorders, or with other alterations related to the chronic use of multiple medications, but these patients are likely to have highly distorted immune responses and present an altered biome (surrounded by hospital germs). Thus, the main objective of this project was to describe the main causes of death in SLE in southwestern Colombia.

Materials and methods

We conducted a retrospective and observational study of case series. The reported cases were identified by the statistics department; a search in our clinical software was made of patients diagnosed with SLE who died in our institution. All the patients included were older than 14 years, fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE, and had died between January 2011 and June 2017 at the Fundación Valle del Lili Hospital in Cali, Colombia [11]. Our institution is a high complexity and referral medical center, which provides care to all sort of patients, regardless of social security status, ethnicity, or socioeconomic class. The Ethics Committee of our institution approved the study. Clinical, laboratory, and treatment-related data were obtained by chart review, including associated variables and their changing values over time. The causes of death were determined by the rheumatologist and intensivists who evaluated the patients and by the two authors (also rheumatologists) according to the death certificate and medical chart.

We summarized the data using statistics of central tendency (mean, median) and dispersion (standard deviation, interquartile range [IQR]) for quantitative variables. We described qualitative variables as frequencies and proportions. We performed all statistical analyses using STATA13® software (StataCorp, College Station, TX, USA).

In addition, we analyzed a subgroup of eight patients (16.3%) with a complete follow-up in our hospital since the initial diagnosis of death. In these cases, we checked all the medical records from 2 years before the death until the outcome of death. The data of each patient were grouped and analyzed in four periods of 6 months each.

Results

During the study period, 1776 SLE patients with an average age of 37 ± 14 years were treated at our center; of these patients, 1577 (88.8%) were women and 199 (11.2%) were men. Forty-nine SLE patients (2.76%) died during the study, and their mean age was 40.6 years (SD 17.4; range 16–46 years). Most of the patients who died were women ($n = 44$, 89.8%). The median disease duration among the patients who died was 4.5 years (IQR 2–8). All the patients were ethnically mixed; six patients were black. We compared the variables associated with clinical and immunological complications between black and non-black patients and found that only disease duration was significantly lower in black patients (p 0.034).

At the time of death, 28/49 patients had an anti-DNA result available that was positive in 19 patients (67.8%), 44 patients (89.8%) presented with lymphopenia, 44 (89.8%) with anemia, 38 (77.5%) with leukopenia, and 36 (73.4%) with thrombocytopenia. Another variable

identified was the low median serum albumin at 2.2 mg/dL (IQR 1.7–2.8).

The most common complication associated with fatality in the patients who died was LN, which occurred in 19 cases (38.77%), and was mostly type IV ($n = 12$). Ten LN patients (52.63%) were being treated with renal replacement therapy. Additionally, the patients presented high activity indexes, calculated using the SLEDAI-2K (median score 19 [IQR 11–39]), at the time of death.

Also, at the time of death, the median number of hospitalization days was 4 days in general wards and 12 days in the intensive care unit (ICU).

Table 1 shows the analyzed clinical, paraclinical, and therapeutic variables.

The main cause of death was lupus activity and lupus-related damage in 22 patients (44.9%), followed by infections in 15 (30.6%). Five deaths (10.2%) were due to other chronic concomitant diseases, four to cardiovascular causes (8.16%),

Table 1 Clinical, paraclinical, and therapeutic characteristics of the deceased patients with SLE

Characteristic	*n* (%)*
Age*	40.6 ± 17.4
Female sex	44 (89.8)
SLE disease duration**	4.5 (2–8)
Previous admissions due to SLE activity	
0	18 (36.73)
1	24 (48.98)
2 or more	7 (14.29)
ICU hospitalization days**	12 (3–30)
Number of days requiring mechanical ventilation**	3 (1–11.5)
Hospitalization days in general wards**	4 (0–19.5)
Characteristics at the time of death, *n* (%)	
SLEDAI**	19 (11–39)
Confirmed lupus nephritis**	19 (38.77)
Positive anti-DNA (%)	19/28 (67.8%)
Creatinine elevation (mg/dL)**	2.3 (1.2–4.4)
Hemoglobin < 12 g/dL	44 (89.8)
Neutropenia (< $1.5 \times 10^3/\mu L$), *n* (%)	21 (42.8)
Lymphopenia (< $1.5 \times 10^3/\mu L$), *n* (%)	44 (89.8)
Thrombocytopenia (< $100 \times 10^3/\mu L$), *n* (%)	36 (73.4)
Associated APS, *n* (%)	15 (30.6)
Associated RA, *n* (%)	7 (14.29)
Associated RP, *n* (%)	7 (14.29)
Other autoimmune diseases, *n* (%)	4 (8.1)
Associated pulmonary hypertension, *n* (%)	14 (28.5)
Systolic pressure of the pulmonary artery by echocardiogram (mmHg)*	57.2 ± 27.2
Associated hyperparathyroidism, *n* (%)	9 (18.3)
PTH (ng/mL)**	56 (29.7–130)
Prednisone dose (mg/day)**	25 (12.5–50)
Methylprednisolone pulses*	1.67 ± 1.41
Cyclophosphamide pulses, *n* (%)	13 (26.53)
Total dose of cyclophosphamide (gr)**	0.5 (0–6)
Patients who received plasmapheresis, *n* (%)	8 (16.3)
Plasmapheresis sessions**	5 (5–6)
Patients who received rituximab, *n* (%)	9 (18.37)
Number of patients who received immunoglobulin, *n* (%)	5 (10.2)

ICU intensive care unit, *APS* antiphospholipid syndrome, *RA* rheumatoid arthritis, *RP* raynaud phenomenon, *SD* standard deviation, *IQR* interquartile range

*Mean ± SD

**Median (IQR)

and three to unclear causes (6.12%) (please see Table 2 for details). After the analysis and review of the death certificate and medical chart by two rheumatologists, none cause of death was changed for any patient.

Among the patients who died due to lupus activity and organ-damage ($n = 22$, 44.9%), eight (16.3%) had catastrophic antiphospholipid syndrome (CAPS) and other severe complications such as alveolar hemorrhage, central nervous system vasculitis, and stroke (intraparenchymal hematoma or other intracranial hemorrhage). One patient had hemophagocytic syndrome.

Regarding the infections in the patients who died, most were bacterial and affected a total of forty cases (81.6%); some patients presented more than one infection. Bacteremia was documented in 15 patients (30.6%), followed by fungal infections in eight patients (16.3%), and viral infections in seven (14.2%). In addition, eight patients presented with bacterial, viral, and fungal infections (16.3%), while five (10.2%) patients presented with bacterial and fungal infections (Table 3). Of the 40 cases, 15 (30.6%) were fatal with sepsis from different foci (abdominal origin, pulmonary, soft tissue, and bacterial endocarditis). One case of infection was secondary to mucormycosis.

Four (8.16%) cases were associated with cardiovascular complications: two had aortic dissection, one had massive pulmonary thromboembolism, and one had congestive heart

Table 2 Causes of death of patients with SLE

Cause of death	*n* (%)*
SLE-associated death	22 (44.9)
CAPS	8 (16.33)
SLE activity	6 (12.24)
Alveolar hemorrhage	2 (4.08)
Central nervous system vasculitis	2 (4.08)
Intracerebral hematoma	1 (2.04)
Brain hemorrhage	1 (2.04)
Hemophagocytic syndrome	1 (2.04)
Stroke	1 (2.04)
Other death causes	27 (55.1)
Infection	15 (30.6)
Sepsis with no clear focus	6 (12.24)
Abdominal sepsis	2 (4.08)
Bacterial endocarditis	2 (4.08)
Pulmonary sepsis, respiratory failure	1 (2.04)
Soft tissue infection	1 (2.04)
Mucormycosis	1 (2.04)
Histoplasmosis	1 (2.04)
Necrotizing fasciitis	1 (2.04)
Other chronic diseases	5 (10.2)
Liver cirrhosis	2 (4.08)
Colon cancer	1 (2.04)
Pulmonary fibrosis	1 (2.04)
Retroperitoneal hematoma	1 (2.04)
Cardiovascular	4 (8.16)
Massive pulmonary embolism	1 (2.04)
Aortic dissection	2 (4.08)
Congestive heart failure	1 (2.04)
Death of unclear cause	3 (6.12)

CAPS catastrophic antiphospholipid syndrome, *SD* standard deviation
*Mean ± SD

Table 3 Infections associated with SLE mortality

Infections	*n* (%)
Bacterial infections	
Unidentified microorganism	20 (40.8)
Bacteremia	15 (30.6)
Urinary tract infection	2 (4)
Pulmonary tuberculosis	2 (4)
Mediastinal wound infection	1 (2)
Colitis due to *Clostridium difficile*	2 (2)
Spondylodiscitis	3 (2)
Secondary bacterial peritonitis	4 (2)
Gastroenteritis due to *Salmonella* sp.	5 (2)
Venous ulcer infection	6 (2)
Pneumonia	7 (2)
Necrotizing fasciitis	8 (2)
Endocarditis due to *E. faecalis*	9 (2)
Subtotal bacterial infections	40 (81.6)
Viral infections	
Cytomegalovirus	2 (4)
Chikungunya	1 (2)
Epstein-Barr	2 (2)
Herpes simplex	3 (2)
Varicella zoster	4 (2)
John Cunningham virus	5 (2)
Subtotal viral infections	7 (14.2)
Fungal infections	
Candidemia	4 (8)
Histoplasmosis	3 (6)
Pneumocystosis	1 (2)
Mucormycosis	1 (2)
Subtotal fungal infections	8 (16.3)
Multiple infections	
Bacterial, viral, and fungal infection	8 (16.3)
Bacterial and viral infection	4 (8.16)
Bacterial and fungal infection	5 (10.2)
Subtotal multiple infections	17 (34.7)

failure. At the time of death, four patients (8%) presented with other chronic diseases as causes of death (liver cirrhosis, colon cancer, and pulmonary fibrosis). In three patients (6.12%), a sudden multisystemic failure with no clear cause occurred; most likely, it was of infectious or cardiovascular origin.

At the time of their deaths, the patients' treatments included oral steroids (median dose, 25 mg/day [IQR 12.5–50]); the average number of methylprednisolone pulses received was 1.67 ± 1.41; 13 patients (26.5%) received pulse cyclophosphamide; 9 (18.3%) received rituximab; 5 (10.2%) intravenous immunoglobulin; and 8 (16.3%) therapeutic plasma exchange with a median of five sessions.

A subgroup of eight patients (16.3%) had a complete follow-up in the institution from the SLE diagnosis to the fatal outcome; the remaining 83.7% of the group ($n = 41$) had irregular follow-ups, mainly due to changes in health services provision sites by insurers. We noted persistently low levels of C3 among the eight patients we fully followed, with a tendency to decrease (the initial value had a median of 73 mg/dL and at the time of death, the median had changed into 53.5 mg/dL IQR 41–100). The SLEDAI scores increased progressively from 6 at the time of diagnosis to 11 at the last follow-ups (IQR 6–14.5) before the admission in which death occurred and to 19 at the time of death (IQR 12–24.5 SD). We also observed the use of cyclophosphamide and increased glucocorticoid doses before the fatal outcome (15 mg of glucocorticoids in the consultation before death vs. 40 mg by the time of death) (Table 4).

Discussion

The main conditions in SLE patients leading to death worldwide are chronic renal failure, cardiovascular disease, and infections [4]. However, the rates and causes of mortality due to SLE in Colombia are unknown. In the present case series, the main cause of death was uncontrolled SLE activity and lupus damage (44.9%), followed by infections (30.6%), other chronic diseases (10.2%), and, to a lesser extent, cardiovascular causes (8.16%). These causes varied according to the patients' ages and disease duration, among other factors. Our findings showed a predominance of SLE activity with a median of 4.5 years of disease in patients who died, similar to studies showing fatal outcomes during the first years of the disease [3]. It should be noted, that our institution is a high-complexity medical center, which provides care to severe patients and we miss out the follow-up of some patients. However, our results differ from those in other series, including that by Merola JF et al. [12], who found a higher proportion of infections as a cause of death and a lower frequency of cardiovascular events than ours. A low frequency of neoplasms is associated with fatal outcomes [3].

A Brazilian study by Costi et al. [13] identified 8761 reports of deaths from SLE, with a mortality rate of 4.76 deaths per 10^5 inhabitants. The main cause of death was "musculoskeletal system and connective tissue disorders" in 77.5%, which they interpreted as SLE activity, followed by circulatory (6%), infectious (2.8%), respiratory (2.2%), and digestive (2.1%) causes.

Men tend to manifest the disease in more severe and sudden forms and have higher mortality rates than women, according to the literature [6]. In our series, the number of men with fatal outcomes was five (10.2%), which corresponds to a mortality of 2.5% in relation to the total population of men reviewed. Women were the main group in our series.

SLE in indigenous and in black ethnic groups decreases survival over time [6, 14]. Historically, Hispanics were thought to have a higher mortality rate; however, a study by Gómez-Puerta JA et al. [15] described the "Hispanic Paradox" in which a 40,000-adult population with SLE in the USA (of whom 6489 were Hispanic) had 41% lower death rates than the white and black populations, probably because

Table 4 Patient subgroup with complete follow-up from SLE diagnosis until death

Complete follow-up ($n = 8$)	Diagnosis	Follow-up 1	Follow-up 2	Death
ER admissions for SLE activity**	0 (0–1)	0 (0–1.5)	0.5 (0–1.5)	1.5 (0–3.5)
C3 consumption (mg/dL)**	73.5 (59–75)	70 (48.15–77.5)	67.5 (45–76)	53.5 (41.6–100.7)
C4 consumption (mg/dL)**	11.5 (7.5–16)	11 (6.4–17.4)	9 (4.6–13)	10.89 (4.5–10)
SLEDAI**	6 (4–11)	8 (5–23)	11 (6–14.5)	19 (12–24.5)
Oral steroid dose (mg/day)**	10 (6.2–15)	12.5 (10–25)	15 (10–35)	40 (27.5–50)
Methylprednisolone pulses **	0 (0–1.5)	0 (0–3)	0 (0–0)	3 (0–7)
Cyclophosphamide pulses, *n* (%)	0 (0)	2 (25)	2 (25)	3 (37.5)
Days hospitalized in general wards**	0 (0–3.5)	3 (0–11)	8 (0–27)	12.5 (2.5–35.5)
Days in the ICU**	0 (0–0)	0 (0–2)	0 (0–0)	11.5 (4–38.5)

ER emergency room, *ICU* intensive care unit, *IQR* interquartile range

**Median (IQR)

the Hispanic population returned to their countries of origin. Mortality studies on SLE in Hispanic populations should be expanded.

Regarding SLE clinical presentation, LN is one of the main risk factors for morbidity and mortality; the frequency of LN presentation is 69% in people of African descent and 61% in people of Hispanic descent. Approximately 10% of LN patients develop terminal renal failure [16]. LN patients have mortality rates of 6–6.8, while those without LN have a mortality rate of 2.4. In our series, 28/49 patients had an anti-DNA result available that was positive in 19 patients (67.8%); anti-DNA was not performed in all patients due to severe commitment. Additionally, 38% of the cases had LN, mostly of type IV (63%), and 20.41% were being treated with renal replacement therapy. These findings differ from another cohort of our institution with 74 SLE patients; 70% of these patients have positive anti-DNA and 30% present LN (unpublished data).

Feldam CH et al. [17] identified 33,565 SLE patients, 7113 of whom had LN. They reported a total of 9078 serious infections among the 5087 SLE patients without LN (15.12%) and 3949 infections in 1825 LN patients (25.6%). Some (19.5%) had two types of infections and others (17.9%) had three or more; most patients presented with pneumonia, cellulitis, and bacteremia. In addition, they reported 33 cases with tuberculosis, 160 with viral infections due to herpes zoster, 27 with aspergillosis, 18 with pneumocystis infection, and 14 with cryptococcosis. The researchers observed an increased risk of infections with the use of glucocorticoids (HR 1.51; 95% CI, 1.43–1.61) and immunosuppressive therapy (HR 1.11; 95% CI, 1.03–1.20) compared with those who did not use either medication. The findings in our population were similar to those described by these researchers: 13 of the 15 patients who died from infections had bacterial infections, corresponding to 26.5% of the total deaths. The original locations of the infections were abdominal, soft tissues, and lungs (in a decreasing order). Polymicrobial infections were found in 16.3% of the cases, with ICU stays longer than 12 days. This result suggests the need to identify the optimal immunosuppression periods to avoid these complications that increase hospital stay and mortality.

In addition, Ichinose et al. developed a multicenter study in Japan to evaluate the predictive factors of long-term mortality in lupus nephritis [18]. They found that the survival rate of patients with LN was associated with complete renal response (CR) and that male gender and a higher index of activity are predictive factors for failure to achieve CR.

In our study, cardiovascular events were the third most common causes of death: aortic dissection (two patients), acute pulmonary thromboembolism (one patient), and congestive heart failure (one patient). We found no cases of death secondary to acute myocardial infarction. In general, cardiovascular events are known to occur more frequently in patients older than 50 [3]; the average age in our study was 40 (± 17.4). Cardiovascular disease in SLE is multifactorial and associated with accelerated atherosclerosis, chronic inflammation, hyperhomocysteinemia, chronic renal failure, antiphospholipid syndrome (APS), and steroid use, among others [14, 19, 20].

APS can be associated with SLE in up to 50% of patients. According to the CAPS registry [21], 30% of the cases with CAPS had SLE with an associated mortality of 48%. In our study, 30% of APS cases were associated with SLE, 16.3% of whom developed CAPS.

SLE patients are also at increased risk of developing malignancies [7]. In a UK series by Rees F et al., the malignancies were the leading causes of death (10–15%) [10]. In our series, only one fatal case was associated directly with a malignancy (colon cancer).

It is important to mention that our study has some limitations, as we described above our institution is a high complexity and referral medical center; thus, we mostly provide care to critical patients. Therefore, our SLE patients might present an early-onset highly active disease and die due to complications. Moreover, we do not have the full medical follow-up of some SLE patients presenting less severe disease and patients that require prolonged renal replacement therapy.

In our study, the patients who died showed persistently high SLEDAI, LN types IV or VI, APS, persistent hypocomplementemia, the need for continuous severe immunosuppression, and prolonged ICU stays. The outcome was associated mainly with SLE activity that was refractory to treatment and infections mainly due to nosocomial bacteria. These variables should be considered in subsequent studies aimed at predicting fatal outcomes in SLE [22]. Knowledge of risk factors may help physicians be alert and develop innovative strategies to improve outcomes.

Compliance with ethical standards

Disclosures None.

References

1. Bernatsky S, Boivin J-F, Joseph L, Manzi S, Ginzler E, Gladman DD, Urowitz M, Fortin PR, Petri M, Barr S, Gordon C, Bae SC, Isenberg D, Zoma A, Aranow C, Dooley MA, Nived O, Sturfelt G, Steinsson K, Alarcón G, Senécal JL, Zummer M, Hanly J, Ensworth S, Pope J, Edworthy S, Rahman A, Sibley J, el-Gabalawy H, McCarthy T, St. Pierre Y, Clarke A, Ramsey-Goldman R (2006) Mortality in systemic lupus erythematosus. Arthritis Rheum 54:2550–2557. https://doi.org/10.1002/art.21955
2. Kasitanon N, Magder LS, Petri M (2006) Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore) 85:147–156. https://doi.org/10.1097/01.md.0000224709.70133.f7
3. Fors Nieves CE, Izmirly PM (2016) Mortality in systemic lupus erythematosus: an updated review. Curr Rheumatol Rep 18(21):21. https://doi.org/10.1007/s11926-016-0571-2
4. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS (2017) Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol 13:799–814. https://doi.org/10.1080/1744666X.2017.1327352

5. Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS (2008) Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology 48:542–545. https://doi.org/10.1093/rheumatology/kep012
6. Andrade RM, Alarcón GS, Fernández M, Apte M, Vilá LM, Reveille JD, LUMINA Study Group (2007) Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. Arthritis Rheum 56:622–630. https://doi.org/10.1002/art.22375
7. Lee YH, Choi SJ, Ji JD, Song GG (2016) Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus 25:727–734. https://doi.org/10.1177/0961203315627202
8. Pons-Estel GJ, Catoggio LJ, Cardiel MH, Bonfa E, Caeiro F, Sato E, Massardo L, Molina-Restrepo JF, Toledano MG, Barile-Fabris LA, Amigo MC, Acevedo-Vásquez EM, Abadi I, Wojdyla D, Alarcón-Riquelme ME, Alarcón GS, Pons-Estel BA (2015) Lupus in Latin-American patients: lessons from the GLADEL cohort. Lupus 24:536–545. https://doi.org/10.1177/0961203314567753
9. Legge A, Kirkland S, Rockwood K, Andreou P, Bae SC, Gordon C, Romero-Diaz J, Sanchez-Guerrero J, Wallace DJ, Bernatsky S, Clarke AE, Merrill JT, Ginzler EM, Fortin P, Gladman DD, Urowitz MB, Bruce IN, Isenberg DA, Rahman A, Alarcón GS, Petri M, Khamashta MA, Dooley MA, Ramsey-Goldman R, Manzi S, Steinsson K, Zoma AA, Aranow C, Mackay M, Ruiz-Irastorza G, Lim SS, Inanc M, van Vollenhoven RF, Jonsen A, Nived O, Ramos-Casals M, Kamen DL, Kalunian KC, Jacobsen S, Peschken CA, Askanase A, Hanly JG (2019) Evaluating the properties of a frailty index and its association with mortality risk among patients with systemic lupus erythematosus. Arthritis Rheum:0–3. https://doi.org/10.1002/art.40859
10. Rees F, Doherty M, Grainge MJ, Lanyon P, Davenport G, Zhang W (2016) Mortality in systemic lupus erythematosus in the United Kingdom 1999–2012. Rheumatology 55:854–860. https://doi.org/10.1093/rheumatology/kev424
11. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725. https://doi.org/10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y
12. Merola J, Bermas B, Lu B, Karlson EW, Massarotti E, Schur PH, Costenbader KH (2014) Clinical manifestations and survival among adults with (SLE) according to age at diagnosis. Lupus 23:778–784. https://doi.org/10.1177/0961203314526291
13. Costi LR, Iwamoto HM, Neves DC de O, Caldas CAM (2017) Mortality from systemic erythematosus lupus in Brazil: evaluation of causes according to the government health database. Rev Bras Reumatol Engl Ed 57:574–582. https://doi.org/10.1016/J.RBRE.2017.09.001
14. Bruce IN, O'Keeffe AG, Farewell V et al (2015) Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 74:1706–1713. https://doi.org/10.1136/annrheumdis-2013-205171
15. Gómez-Puerta JA, Barbhaiya M, Guan H, Feldman CH, Alarcón GS, Costenbader KH (2015) Racial/ethnic variation in all-cause mortality among United States Medicaid recipients with systemic lupus erythematosus: a Hispanic and Asian paradox. Arthritis Rheum 67:752–760. https://doi.org/10.1002/art.38981
16. Almaani S, Meara A, Rovin BH (2017) Update on lupus nephritis. Clin J Am Soc Nephrol 12:825–835. https://doi.org/10.2215/CJN.05780616
17. Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, Costenbader KH (2015) Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheum 67:1577–1585. https://doi.org/10.1002/art.39070
18. Ichinose K, Kitamura M, Sato S, Fujikawa K, Horai Y, Matsuoka N, Tsuboi M, Nonaka F, Shimizu T, Fukui S, Umeda M, Koga T, Kawashiri S, Iwamoto N, Tamai M, Nakamura H, Origuchi T, Nishino T, Kawakami A (2019) Factors predictive of long-term mortality in lupus nephritis: a multicenter retrospective study of a Japanese cohort. Lupus 28:295–303. https://doi.org/10.1177/0961203319826690
19. Agarwal S, Elliott JR, Manzi S (2009) Atherosclerosis risk factors in systemic lupus erythematosus. Curr Rheumatol Rep 11:241–247
20. Turesson C, O'Fallon WM, Crowson CS et al (2003) Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 62:722–727. https://doi.org/10.1136/ARD.62.8.722
21. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, Cervera R, CAPS Registry Project Group (European Forum on Antiphospholipid Antibodies) (2016) Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev 15:1120–1124. https://doi.org/10.1016/J.AUTREV.2016.09.010
22. Ocampo-Piraquive V, Nieto-Aristizábal I, Cañas CA, Tobón GJ (2018) Mortality in systemic lupus erythematosus: causes, predictors and interventions. Expert Rev Clin Immunol 14:1043–1053. https://doi.org/10.1080/1744666X.2018.1538789