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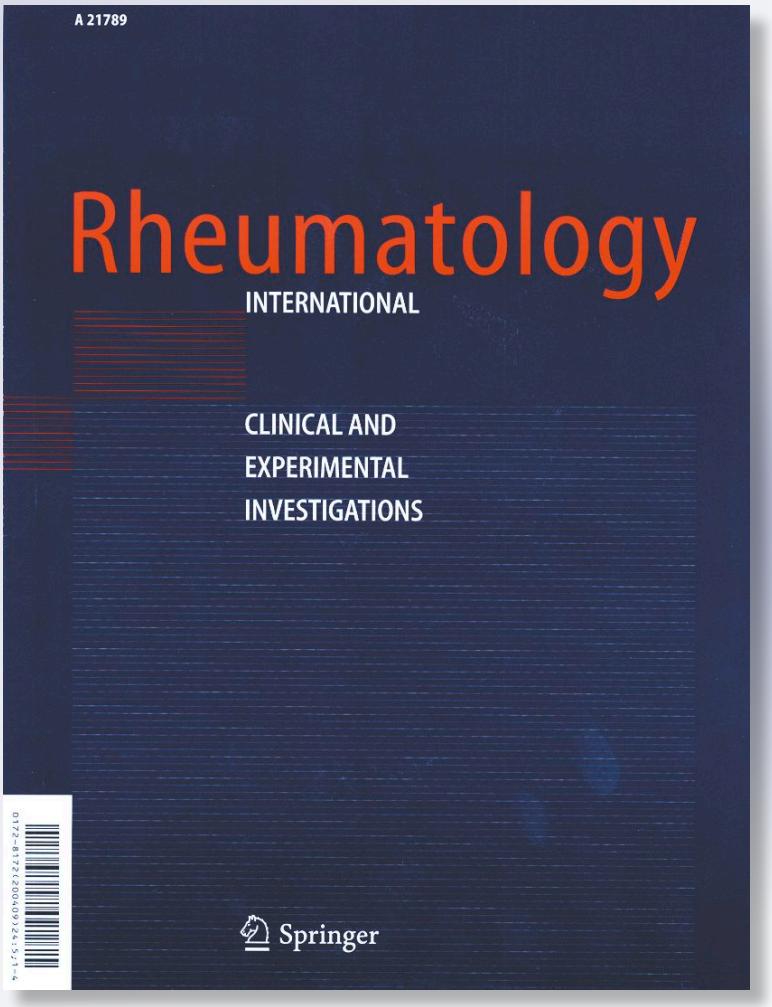

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ORIGINAL ARTICLE

Causes and predictors of death in Brazilian lupus patients

Rosa Weiss Telles · Cristina Costa Duarte Lanna · Fabiana Lemos Souza · Luciana Andrade Rodrigues · Rodrigo Citton Padilha Reis · Antonio Luiz Ribeiro

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Abstract The objective of this study is to determine the causes and predictors of death in systemic lupus erythematosus (SLE) patients. Causes of death were defined based on death certificates, medical records, and information collected from doctors and relatives. Possible variables predicting mortality were assessed by Kaplan–Meier and Cox regression methods. The multivariate model was validated using the *bootstrap* method, and the hazard ratios were adjusted according to the *shrinkage* coefficient. One hundred eighty-one patients were included, and two patients were lost to follow-up. The median (IR) age at T_0 and disease duration of the 179 patients were 26.7 (21.8–34.6) and 8.2 (4.3–12.4) years, respectively. After a median (IR) follow-up of 3.3 (3.1–3.5) years, 13 (7.3 %) patients died due to end-organ failure (5), infection (5), disease activity (1), and atherosclerotic cardiovascular disease (CVD) (1). The cause of mesenteric ischemia in one patient could not be determined. Predictors of mortality collected at T_0 were the following: nephritis, chronic kidney disease, antiphospholipid syndrome (APS), higher modified SLEDAI-2k, higher damage index score, intravenous cyclophosphamide use, higher daily dose of prednisone, and higher systolic blood pressure. Independent predictors of mortality were higher damage index score (HR: 1.40; 95 % CI: 1.08–1.82), cyclophosphamide use (HR: 3.80; 95 % CI: 1.13–12.77), and APS diagnosis (HR: 3.82; 95 % CI: 1.07–13.59). This paper presents a high frequency of late mortality in lupus patients due to the SLE itself and infection. This result is not in agreement with the initial proposed bimodal pattern of lupus mortality, nor is it in agreement with the high frequency of CVD as a cause of death in developed countries. The most important predictors of death were related to the lupus itself.

Keywords Systemic lupus erythematosus · Mortality · Survival · Causes of death · Predictors of death

Introduction

The 5-year survival rate in patients with systemic lupus erythematosus (SLE) has significantly improved in developed countries over the last few decades, from less than 50 % in the 1950s to more than 90 % in recent years [1–6]. However, the survival rates in developing countries are substantially lower, reaching 72 % with few exceptions [7, 8].

The improvement of SLE survival may be attributed to a number of factors, including the early diagnosis of lupus due to the wider availability of specific tests, the more judicious use of corticosteroids and cytotoxic agents, and the improved supportive treatment options (antibiotics, antihypertensive drugs, dialysis, and renal transplantation) [1, 2, 9, 10].

Although the life expectancy in SLE has increased, the mortality remains higher than that in the general population, with a standardized mortality ratio (SMR) of 2.4 [9]. The strata of the SMR show that the highest rates of mortality are found in young patients <40 years old (SMR = 6.4) and with early disease <1 year (SMR = 7.7) [9].

In 1976, Urowitz et al. [11] first described the bimodal pattern of the mortality curve in lupus patients, highlighting the importance of atherosclerotic cardiovascular disease (CVD) as a cause of late death (with mean lupus duration of 8.6 years) in five patients. Such a bimodal

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pattern has since been reported in many large series worldwide. According to this pattern, many early deaths (<2 years from time of diagnosis) are due to active disease and infections, but deaths taking place >5 years after diagnosis are often attributable to cardiovascular events [1, 5, 12, 13]. This scenario is possibly changing in the industrialized world. A European multicenter study recently demonstrated that the bimodal mortality curve has flattened out and that the mortality risk is nearly stable over time in that continent [14]. In addition, the authors reported that almost one-third of fatalities occurred while the SLE was in remission. Fatalities were most often due to an intricate mix of disease activity and accrued damage with intercurrent infections and cardiovascular events.

The most important causes of death in SLE are infections, cardiovascular events, malignancy and active or latent lupus. Bernatsky et al. demonstrated in a multinational lupus cohort that the SMR due to circulatory disease tended to increase slightly from the 1970s to the year 2001 in industrialized countries. In this same period, the SMR due to infections and renal disorders dramatically decreased [9]. Data are scarce in developing countries, and infections and active disease seem to remain as the main causes of death throughout the illness [7, 15, 16].

In this study, we analyzed both the cause of death in a cohort of lupus patients attending at a Brazilian university hospital as well as the risk factors for death in those patients.

Patients and methods

This prospective, observational study was carried out at the Rheumatology Department of the *Hospital das Clínicas* of the *Universidade Federal de Minas Gerais/Brasil (UFMG)*. This study was approved by the Human Research Ethics Committee/*UFMG* and by the Board of Education, Research and Extension of the *Hospital das Clínicas/UFMG*.

Patients

During the period between May 2005 and February 2006 (T_0), the patients seen at the SLE outpatient clinic were consecutively included in a prospective study of cardiovascular disease in lupus [17, 18] according to the following criteria: diagnosis of SLE as per the American College of Rheumatology (ACR) (1982/1997) classification criteria [19, 20], aged 18 years or older, and completion of a signed informed consent form. One hundred eighty-one patients were included, and all of them had at least one visit at the clinic after the inclusion period and were considered for the mortality analysis. Of those, two patients lost contact with the clinic and were excluded. Seven other patients were lost to follow-up but were alive at the end of the study (contacted by telephone) and were censored at their last visit to the outpatient clinic. The end of the observation period was between October 2008 and July 2009.

Protocol

Baseline demographics, lupus characteristics and manifestations of cardiovascular disease and risk factors for coronary artery disease (CAD) were obtained from each patient at the first study visit (T_0) by one of the authors (RWT) according to a previously published protocol [17, 18]. Photosensitivity, mucosal ulcers, malar rash, and discoid lupus were considered together as mucocutaneous manifestations. The activity of the disease was quantified using a modified SLEDAI-2k (excluding the serologic variables anti-dsDNA and complement dosing) [21, 22]. Sequelae secondary to SLE or its treatment were assessed according to the damage index proposed by the SLICC/ACR (SDI) [23]. The antiphospholipid antibody syndrome (APS) was defined according to the preliminary criteria of Sapporo [24]. Renal function was estimated from the calculation of creatinine clearance, following the Cockcroft–Gault formula [25]. Stage 3 or greater chronic kidney disease (CKD) was defined as creatinine clearance (CrCl) < 60 mL/min/1.73 m^2.

The cause of death was ascertained by a review of hospital files, death certificates, and by a discussion with the doctor and/or relatives who cared for the patient during the terminal stage of illness. The primary cause of death was categorized as lupus activity, end-stage organ failure due to lupus, infection, atherosclerotic cardiovascular disease (CVD), and unknown causes. The primary cause of death was defined as the main clinical or pathological process directly responsible for death.

Statistical analysis

The categorical data were presented as numbers (%) and the continuous variables as mean and standard deviation (SD) or median and interquartile range (IR) according to the distribution.

The associations between the dichotomous variables considered possible risk factors for death and mortality were assessed by Kaplan–Meier estimation of survival curves (compared by the log-rank test). The associations of continuous variables and death were assessed by proportional hazards Cox regression.

Multivariate analysis was performed using the Cox proportional hazard model to identify independent risk factors for poor survival. Variables with $p < 0.15$ in the

univariate analysis and those with clinical relevance or prior data in the literature were included in the models. Considering the small sample size and the low frequency of events, statistical techniques were used to protect the final model from *overfitting* and *optimism*. Therefore, the internal validation of the final model chosen for clinical and biological plausibility was performed by using 199 *bootstrap* samples after the *c* and R^2 statistic of the original model and all the *bootstrap* samples were obtained. The adjustment for *overfitting* was done by reducing the coefficients of the final model and the corresponding hazard ratios (HR) by the coefficient shrinkage *s* calculated by the formula $s = (\text{model } \chi^2 - df)/\text{model } \chi^2$ [26].

A p value of <0.05 (two-sided) was considered as statistically significant.

Statistics were performed using the SPSS statistical package version 12.0 and the R Project program using the package Design (WWW.r-project.org).

Results

The final study sample consisted of 179 patients; 174 (97.2 %) were women. The median (IR) age at baseline (T_0) was 38 (29–46) years and at lupus diagnosis was 26.7 (21.8–34.6) years. The median (IR) disease duration at T_0 and at follow-up at the department were 8.2 (4.3–12.4) years and 6.8 (4.4–10.8) years, respectively.

The main clinical manifestations and laboratory abnormalities during lupus follow-up and at T_0 are shown in Table 1. All patients were ANA-positive, and 138 of them (77.1 %) met the following immunologic criteria: 89 (49.7 %) were anti-dsDNA positive, 50 (27.9 %) anti-Sm positive, 26 (14.5 %) lupus anticoagulant positive, 49 (27.4 %) anticardiolipin positive, and 16 (8.9 %) false VDRL positive. At T_0, 16 patients (8.9 %) had CKD stage 3, and 11 patients (6.1 %) had APS.

During the observation period of 3.3 (3.1–3.5) years, 13 (7.3 %) patients died (Table 2). The median (IR) of age at the time of death of these 13 patients was 44.8 (40.8–55.8) years, and the median (IR) of disease duration was 9.6 (7.6–19.3) years.

The cause of death was ascertained by a review of hospital files (7 patients), by death certificates (2 patients), and through a discussion with the doctor and/or relatives who cared for the patient during the terminal phase of illness (4 patients). The primary causes of death were mainly end-stage organ failure due to lupus (pulmonary hypertension in two patients and CKD in three patients) and infections (5 patients), followed by lupus activity and CVD (1 patient each) (Fig. 1). One patient died of mesenteric ischemia of unknown cause. This patient was being treated for lupus nephritis with cyclophosphamide and had hypertension and hypertriglyceridemia as risk factors for CAD. The patient had no diagnosis of APS and was negative for antiphospholipid antibodies. It is noteworthy that of the five patients who died from infection, three showed signs of significant inflammatory activity of SLE. Moreover, except for one male patient who died within 4.4 years of his diagnosis of SLE, all other deaths occurred late, that is, with five or more years of illness.

Table 1 Clinical and laboratory features of SLE in 179 patients, Hospital das Clínicas/UFMG, 2008–2009

SLE features	During SLE follow-up N (%)	T_0 N (%)
Mucocutaneous manifestations	155 (86.6)	37 (20.7)
Serositis	53 (29.6)	1 (0.6)
Arthritis	122 (68.2)	11 (6.1)
Nephritis	118 (65.9)	37 (20.7)
Nephrotic proteinuria (> 3.5 g/24 h)	37 (20.7)	5 (2.8)
Neuropsychiatric manifestations	22 (12.3)	0
Hematological abnormalities	166 (92.7)	81 (45.3)
Hemolytic anemia	36 (20.1)	3 (1.7)
Thrombocytopenia	35 (19.6)	1 (0.6)
Lymphopenia	163 (91.1)	77 (43)
Leucopenia	89 (49.7)	31 (17.3)
Skin vasculitis	78 (43.6)	7 (3.9)

The age of SLE diagnosis (HR: 1.03; 95 % CI: 0.98–1.09; $p = 0.232$) and the duration of disease (HR: 1.06; 95 % CI: 0.98–1.15; $p = 0.128$), and of clinical follow-up (HR: 1.01; 95 % CI: 0.91–1.13; $p = 0.822$) were not significantly associated with risk of death. There was a trend between the age at T_0 and the risk of death during the study follow-up (HR: 1.05; 95 % CI: 1.00–1.10; $p = 0.051$).

Among the SLE characteristics present at T_0, the following were risk factors for death at the univariate analysis (log-rank test): nephritis ($p = 0.006$), stage 3 or greater CKD ($p < 0.001$), and APS ($p < 0.001$) (Fig. 2).

It was not possible to estimate the modified SLEDAI-2K of two patients at baseline. The median (IR)-modified SLEDAI-2k of the remaining 177 patients was 0 (0–4). There were higher modified SLEDAI-2k measures at T_0 among the deceased than among the surviving patients (HR: 1.12; 95 % CI: 1.01–1.25; $p = 0.040$). Likewise, the SDI scores were higher among the deceased than among the surviving patients, and these differences were statistically significant (HR: 1.57; 95 % CI: 1.23–2.01; $p < 0.001$). An initial SDI ≥ 3 [27] significantly increased the risk of death (log-rank: $p < 0.001$) (Fig. 3).

As for the treatment of SLE, 79.3 % patients were receiving prednisone at T_0, 50.3 % were using antimalarial agents, and 46.4 % were using some type of immunosuppressant (intravenous cyclophosphamide, 12.3 % and

Table 2 Characteristics and causes of death of 13 lupus patients, Hospital das Clínicas/UFMG, 2008–2009

Patient	Gender	Age of death (years)	Disease duration (years)	Primary cause of death (location)	Classification
1	F	59	30.0	Sudden death (residence)	CVD** (CABG–Stroke–PAD)
2	F	44	19.3	Hipoxic-ischemic encephalopathy (hospital/HC)	Infection* (respiratory infection)
3	F	52	29.8	Sepsis (hospital)	Infection** (osteomyelitis)
4	F	33	8.1	Sepsis (hospital)	Infection** (pyelonephritis)
5	F	41	7.7	Sepsis (hospital)	Infection* (respiratory infection)
6	F	47	6.0	Sudden death (residence)	SLE end-stage organ failure (pulmonary hypertension)
7	F	41	15.2	Sudden death (hospital/HC)	SLE end-stage organ failure (pulmonary hypertension)
8	F	40	22.5	Neurogenic and distributive shock (hospital/HC)	SLE activity (TTP?)
9	M	57	4.4	Mesenteric ischemia (hospital)	Undefined*
10	F	33	9.9	Sepsis (hospital/HC)	Infection* (urinary sepsis)
11	F	56	8.2	Ventricular fibrillation (hospital)	SLE end-stage organ failure (ESRD)
12	F	28	5.2	Acute pulmonary edema (hospital)	SLE end-stage organ failure (ESRD)
13	F	58	19.6	Undefined (residence)	SLE end-stage organ failure (ESRD)

HC Hospital das Clínicas/UFMG, *CABG* coronary artery bypass grafting, *CVD* atherosclerotic cardiovascular disease, *PAD* peripheral artery disease, *CNS* central nervous system, *TTP* thrombotic thrombocytopenic purpura, *ESRD* end-stage renal disease

* Clinical and laboratory evidence of activity; ** without clinical and laboratory evidence of activity

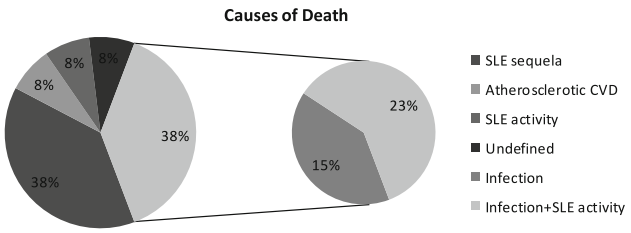

Fig. 1 Causes of death in 13 SLE patients

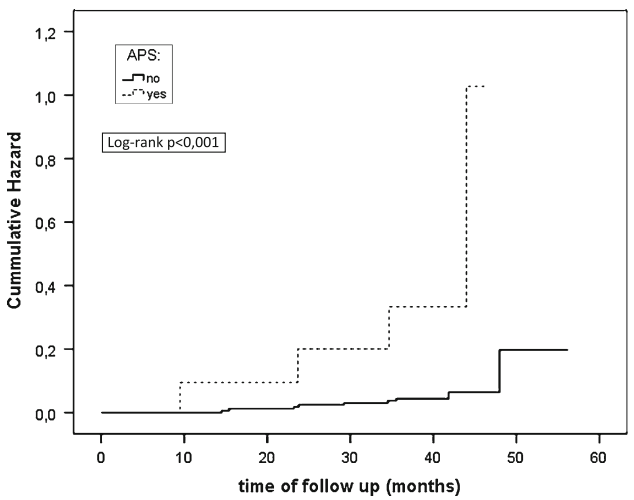

Fig. 2 Kaplan–Meier estimation of hazard ratio curve for secondary antiphospholipid antibody syndrome at T_0

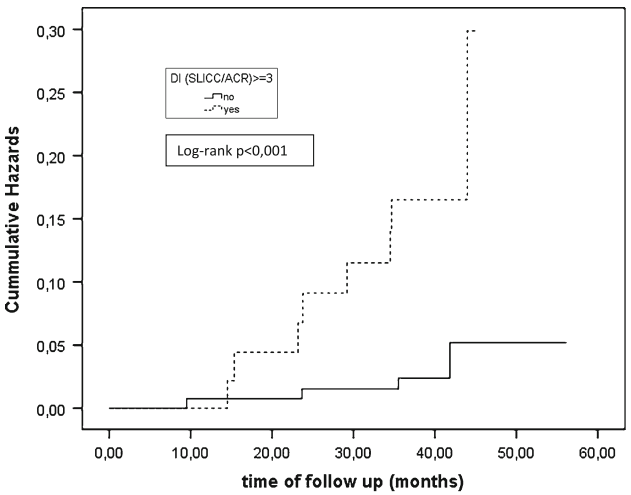

Fig. 3 Kaplan–Meier estimation of hazard ratio curve for damage index score ≥3 at T_0

azathioprine, 22.3 %). The median (IR) cumulative prednisone dose of the entire cohort was 38.4 (23.7–53.2) g and the median (IR) prednisone dose at T_0 was 5 (2.5–10.0) mg/day. The treatment variables at T_0 associated with poor survival were intravenous cyclophosphamide use (log-rank: $p = 0.020$) (Fig. 4) and higher daily prednisone dose (HR: 1.04; 95 % CI: 1.01–1.08; $p = 0.025$). The prednisone dose at T_0 of the patients that remain alive at the end of the study was 5 (2.5–10.0) mg/day *versus* 10 (3.8–20.0) mg/day of the deceased.

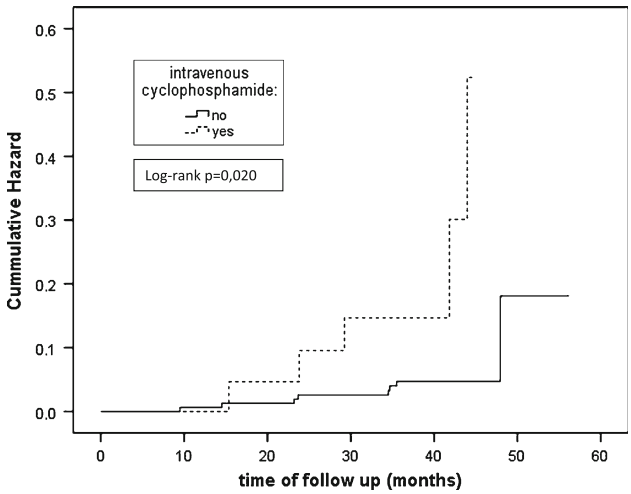

Fig. 4 Kaplan–Meier estimation of hazard ratio curve for intravenous cyclophosphamide at T_0

Table 3 Multivariable Cox regression model, Hospital das Clínicas/UFMG, 2008–2009

Variables at T_0	*B*	HR*	95 % CI**
Damage index (*SLICC/ACR*)	0.41	1.40	1.08–1.82
Intravenous cyclophosphamide	1.63	3.80	1.13–12.77
Antiphospholipid antibody syndrome	1.64	3.82	1.07–13.59

* HR = adjusted hazard ratio; ** 95 % CI = 95 % confidence interval

Model qui-square = $p < 0.001$, degrees of freedom: 3

Among the cardiovascular risk factors for CAD analyzed, higher systolic blood pressure at T_0 (HR: 1.04; 95 % CI: 1.02–1.06; $p < 0.001$) was the only risk factor for death.

A multivariate Cox regression model, with HR (95 % CI) corrected by the *shrinkage* coefficient, is shown in Table 3. The variables at T_0 consistently found to significantly affect mortality in this cohort include intravenous cyclophosphamide use (HR: 3.80; 95 % CI: 1.13–12.77), secondary APS diagnosis (HR: 3.82; 95 % CI: 1.07–13.59), and higher SDI (HR: 1.40; 95 % CI: 1.08–1.82).

Discussion

In the present study at a university hospital in Brazil, thirteen patients (7.3 %) with SLE died during a follow-up of 3.3 (3.1–3.5) years after a median disease duration of 9.6 years. This type of mortality data in developing countries, including Brazil, is scarce. In a study conducted at the *Universidade Federal do Rio de Janeiro* (Rio de Janeiro/RJ, Brazil), Cardoso et al. [27], after 6.3 years of follow-up of 105 lupus patients, found a mortality of 18 %. Such a mortality rate, apparently higher than the one found in the present study, was described in a group of older patients (median age at T_0 of 41 years *versus* 38 years in this study) and a longer duration of SLE (10.6 vs. 8.2 years). Unfortunately, the survival rate could not be calculated in either of the studies due to their design. Appenzeller and Costallat described a 5-year survival rate of 88 % in 509 patients receiving care at the *Hospital das Clinicas* of *UNICAMP* (Campinas/SP, Brazil) during 3.1 (3.5) years of follow-up [28]. This survival is lower than that reported in industrialized countries from the 1990s, where the 5-year survival rate reached more than 95 % in inception cohort studies [2–4, 29, 30]. This difference in mortality rate is possibly related to inherent ethnic differences in disease severity between Brazilians and individuals from other countries. More importantly, the different mortality rates probably reflect the differences in overall standard of living, health-care services, and health-care priorities, factors previously associated with poor survival in lupus [1, 8, 31, 32].

The primary value of this study is its description of causes and predictors of death in lupus patients in a developing country. Despite the increasing frequency of cardiovascular events as cause of death in industrialized countries, infections and lupus itself are the two most important causes of death associated with SLE in the present and in other studies [8, 9]. In fact, even in the developed world, the risk that a lupus patient will die because of an infection is 5 times higher than for a person from the general population; this risk is 7.9 times higher when renal disease is considered as a cause of death [9]. Iriya et al. [33] reported that 58 % of Brazilian lupus patients had an infection as the major cause of death after studying 113 autopsies. In another Brazilian cohort, 43.1 % of 58 deaths in 509 lupus patients were due to sepsis [28].

The results of the present study reinforce the association between lupus activity and infection [34], because three of the five patients who died from an infection also had signs of important inflammatory activity. Furthermore, these 3 patients were taking immunosuppressive drugs (2, cyclophosphamide and 1, azathioprine), a known risk factor for infections in lupus [10].

Despite the late deaths described here, considering that the median duration of disease was greater than 5 years in 92 % of the patients who died, CVD was the primary cause of death in only one person. This finding contradicts the data described in the developed world, particularly the second peak of the bimodal mortality curve proposed by Urowitz et al. [11], where the main causes of death in late lupus were cardiovascular events, especially myocardial infarction. Atherosclerosis seems to be a multifactorial process with traditional and non-traditional risk factors for CAD, including a role for factors associated with the lupus itself [35, 36]. The high frequency of traditional risk factors

for CAD in this cohort has already been published [17, 18]. The high systolic blood pressure at T_0 was the only traditional risk factor for CAD that conferred an increased mortality risk in this study. However, in the multivariate analysis, conditions associated with SLE supplanted the importance of this variable in determining the risk of death.

The assessment of morbidity in lupus has been greatly enhanced by the use of the widely accepted SDI, which records irreversible damage attributable to lupus or its treatment in 12 organs/systems [23]. The renal component is a very important item of the SDI, not only because of the high score that can be reached but also because of the high frequency of nephritis and its consequences in lupus patients. In this present cohort, among 47 patients with an SDI $\geq$ 3, 16 (34 %) had nephritis at T_0, 10 (21.3 %) had CKD at stage 3 or greater, and 16 (34 %) had a history of nephrotic proteinuria during lupus follow-up at the department. Studies using SDI have demonstrated that damage predicts further damage and that a longer disease duration is associated with higher damage scores [37]. In the present cohort, each one-point increase in the initial SDI conferred an approximately 40 % excess mortality risk, and the SDI was an independent prognostic factor as it has been in other studies [27, 31, 38, 39]. Furthermore, the use of cyclophosphamide was an independent risk factor for death. Taken together, the SDI and the intravenous cyclophosphamide were used to identify severe lupus. Beyond the association of cyclophosphamide with infections [34], this immunosuppressive drug is used to treat severe nephritis, another known prognostic factor in SLE frequently found in this cohort [6]. In this work, the univariate analysis identified nephritis as a risk factor for death, but this variable was supplanted by the SDI and by cyclophosphamide use in the multivariate analysis as prognostic factors.

Despite the absence of thromboembolic events (without atherosclerosis or vasculitis) as a proven cause of death, the APS was more frequent in patients who died. The APS is associated with increased SDI and shorter survival [40], and the presence of antiphospholipid antibodies is associated with CKD in patients with biopsy-proven lupus nephritis and with death [3, 10]. In this series, only one patient with terminal CKD had a previous diagnosis of APS, and the diagnosis of the syndrome was not associated with the SDI scoring [with APS: 1 (0–3) vs. without APS: 2 (0–2.5); $p = 0.710$]. Interestingly, APS was present in the patient who had sudden death, likely related to atherosclerosis, confirming the previous literature linking APS with cardiovascular events [41].

In conclusion, the present study described a high frequency of late death associated with infections and with lupus itself in 179 lupus patients prospectively followed up in a university hospital in Brazil. In this cohort, despite the high prevalence of cardiovascular risk factors, atherosclerotic cardiovascular events did not emerge as a major cause of death. Longitudinal studies with adequate sample size and long-term follow-up, preferably with a multicenter study population, are needed to confirm the findings obtained in this study and, eventually, to clarify the possible causes of the differences in the natural history and mortality associated with SLE in developing countries, compared with the developed ones.

Conflict of interest The authors declare that they have no conflict of interest.

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