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ORIGINAL ARTICLE

Survival analysis of patients with systemic lupus erythematosus in a tertiary hospital in southern Brazil

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Abstract Systemic lupus erythematosus (SLE) treatments progress over the years. However, the mortality remains higher than in the general population. Few studies have examined SLE patients' survival in Brazil. This study aims to identify the main characteristics and risk factors to predict mortality and recognize the main causes of death in Brazilian patients with SLE. We retrospectively assessed clinical, demographic, and serological characteristics from 600 patients followed since 2001 in SLE outpatient clinic from Hospital de Clínicas de Porto Alegre. Risk factors for mortality were examined by univariate and multivariate Cox proportional hazards regression analyses. A $p < 0.05$ was considered significant. There were 527 survivors (87.83%). The main causes of death were cardiovascular disease (17%), infection (17%), and infection and SLE activity (17%). Risk factors for death were age at diagnosis (HR 1.065, CI 95% 1.039–10.092), SLICC damage index (HR 1.299, CI 95% 1.076–1569), antiphospholip syndrome (HR 3.021, CI 95% 1.307–6.985), and metilprednisolone pulse (HR 2.628, CI 95% 1.283–5.383). Antimalarials was a protective factor for death (HR 0.191, CI 95% 0.064–0.570). Cardiovascular disease, infection, and SLE activity associated with infection were the main known causes of deaths in our SLE patients. Secondary antiphospolipid syndrome, highest score in SLICC damage index, advanced age at diagnosis, and high dose of corticosteroids were risk factors for mortality. Antimalarials was an important protective factor.

Keywords Mortality · Survival · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory chronic polymorphic disease characterized by activity and remission period. Although treatment has progressed over the past decades, SLE patients still have a higher mortality rate than in the general population [1]. The main causes of death in SLE patients over the world [2, 3] include cardiovascular events, infections, and SLE activity [4]. Knowledge about the causes of death and morbidity relating to SLE is crucial for following therapy and assessment of patients, as well as to contribute to increase the understanding of the disease. Combined with that, few studies have examined SLE patient survival and predictors of death in the Brazilian population [1, 5]. But it is already known that baseline and accrued damage increase mortality risk in Brazilian patients with SLE [1].

The aims of this study are to determine survival and identify the main characteristics and risk factors to predict mortality and recognize the main causes of death in Brazilian patients with SLE.

Methods

Patients

It was retrospectively assessed characteristics from 600 patients in a rheumatology outpatient clinic from Hospital de Clínicas de Porto Alegre which is located in southern Brazil and is a local reference center in rheumatology. The patients were consecutively followed from their first visit after January 2003 until death, lost of follow-up or end of the study in December 2014.

All patients met the American College of Rheumatology revised criteria for classification of SLE [6]. Only 19 (3.2%) of these patients lost follow-up during study period.

Medical consultation and medical chart review were used to collect demographic, clinical, and laboratory data. During the study, the patients were evaluated using a standardized questionnaire for the following variables: age, gender, age at diagnosis, smoking status, other autoimmune diseases, body mass index (BMI), and treatment performed. Clinical manifestations of SLE included the presence of photo sensitivity, malar rash, discoid rash, oral or nasal ulcers, arthritis, serositis (pleuritis or pericarditis), nephritis, and neurological disease, defined as seizures or psychosis. The laboratory evaluation included the presence of hematological disorders (hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia), positive antinuclear antibody (ANA) (titer > 1:80), anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, anticardiolipin, lupus anticoagulant, and false positive VDRL. Patients were also evaluated in regard to secondary antiphospholipid syndrome (SAPS) and secondary Sjogren's syndrome, according to the classification criteria for both diseases [7, 8]. SLEDAI and the SLICC damage index were applied to each patient as a measurement of disease activity and cumulative damage, respectively [9, 10].

The causes of death were collected from electronic medical chart review or by phone calls to relatives and were grouped in: infection and/or disease activity, cardiovascular disease and thromboembolic events, cancer and not known. Cardiovascular disease and thromboembolic events were defined as at least one of the following: coronary artery disease, stroke, transient isquemic attack, peripheral arterial disease, venous or arterial embolism. SLE activity was considered if was need to start or increase the dose of corticoid therapy because of SLE activity and by impression of the assistant rheumatology team. Infection was considered if the patient was under antibiotics treatment recently started and or modified. When it was not possible to distinguish between infection and disease activity, both alternatives were considered as cause of death.

Statistical analyses

Categorical data were presented as percentage and the continuous variables as mean and standard deviation or median. Survival in 30 years was assessed through Kaplan-Meier method. Possible variables predicting mortality which are listed in Table 1 were assessed by Cox regression methods. The multivariate analysis was performed to identify independent risk factors for poor survival. Variables with $p < 0.20$ in the univariate analysis and those with clinical relevance were included in the models. Then, a stepwise backward strategy was used to identify the important variables which were considered those with a $p < 0.10$. A p value of <0.05 was considered significant. Statistics were performed using the SPSS statistical package version 18.

Results

Clinical, demographic, and treatment features of the patients were summarized in Table 1. Disease duration was calculated at the end of the follow-up. Interestingly, the survivors had longer disease duration and were younger when SLE was diagnosed than non-survivors. Survivors had less accrued damage, lower SLEDAI, and were European descent mostly. They also had less cardiovascular disease, diabetes, and SAPS. Non-survivors were more exposed to metylprednisolone pulse therapy and used less hydroxicloroquine than survivors.

The mean survival in this Brazilian population was 35.8 years after diagnosis (CI 95% 32.9–38.7). The survival rate was 96, 93.6, and 78% in 5, 10, and 30 years of disease, respectively, (Fig. 1) in our population.

After multivarariate analysis, the risk factors identified for death were advanced age at SLE diagnosis, more cumulative damage defined as highest SLICC damage index, SAPS and the need of high dose of corticosteroids during the treatment. Not surprisingly, the use of antimalarials was appointed as a protective factor for death (Table 2).

The most common causes of deaths in our patients are shown in Fig. 2. The main identified causes of death were cardiovascular disease, infection, and SLE activity associated with infection. Unfortunately, a high number of non-identified cause of death were noticed.

Discussion

In this singular Brazilian population, from a reference rheumatology center, the risk factors identified which influenced mortality in patients with SLE were SAPS, highest score in SLICC damage index, advanced age at diagnosis, and the need of high dose of corticosteroids. The main causes of death were infection, SLE activity, and cardiovascular disease.

Table 1 Baseline features of survivors and non-survivors patients with systemic lupus erythematosus in 30 years

Variables	Non-survivors $n = 54$ (100%)	Survivors $n = 527$ (100%)	p value[a]
European-derived	31 (64.5)	389 (75.5)	0.02
Female	42 (87.5)	493 (92.4)	0.10
Age at diagnosis[b]	39.3 ± 15.7	33.3 ± 13.9	<0.001
Disease duration[b]	8.6 ± 7.1	11.6 ± 8.8	<0.001
Last SLEDAI[c]	2 (0–7)	1 (0–4)	0.02
SLICC damage index[c]	2 (1–3)	1 (0–2)	0.009
Organ involvement			
Arthritis	35 (72.9)	394 (74.6)	0.06
Nephritis	21 (43.7)	211(40.0)	0.60
Neurologic disorders	7 (14.5)	58 (11.0)	0.60
Hematologic disorders	38 (79.1)	401 (75.8)	0.30
Comorbidities			
Cardiovascular disease	18 (41.8)	80 (15.9)	0.001
Hypertension	36 (76.5)	279 (53.5)	0.02
Diabetes	10 (22.2)	34 (6.5)	0.001
Antiphospholipid syndrome	8 (18.0)	31 (6.7)	0.003
SLE treatment			
Methylprednisolone pulse therapy	20 (42.5)	140 (28.7)	0.03
Cyclophosphamide	17 (35.4)	143 (28.1)	0.30
Methotrexate	8 (17.0)	95 (18.7)	0.50
Azathioprine	18 (39.1)	240 (46.9)	0.20
Antimalarials	44 (91.6)	507 (97.5)	0.001
Mycophenolate mofetil	5 (11.9)	33 (6.4)	0.20
Cyclosporin	0 (0)	3 (5.8)	0.50
Rituximab	0 (0)	5 (9.7)	0.50

[a] Chi-square test for qualitative variables and Mann–Whitney for asymmetric quantitative variables or Student's t test for symmetric quantitative

[b] Years ± standard deviation

[c] Median (interquartile range)

When looking for mortality rate data, one have to keep in mind the wide heterogeneity across race, sex, and country [11]. Estimate of mortality rate in developing countries are poor and of great variability. Two Brazilian cohorts published earlier reported different results. Both of them described patients University hospitals like us. Telles et al. demonstrated a 7.3% mortality rate in 3 years of follow-up [5], but Cardoso et al. had a 18% mortality in 6.3 years [1]. In South Africa, also a developing country, have even worst outcomes demonstrating a 5-year survival rate of 57–72% [12]. In our population, only 4% died in the first 5 years of follow-up similar to Chinese population [13]. Our results are also comparable to those from the Latin American Group for the study of Lupus (GLADEL) population [14] reaching accordance with results in developed countries [15–18].

Ruiz-Irastoza et al. [17] also found SAPS and older age at diagnosis as predictor of mortality in SLE patients like our results. In Birmingham, SLE cohort damage accrual was predictor of death during the follow-up [19].

In a distinct Brazilian population, smaller than ours and with 7 years of follow-up, the baseline and damage accrued during the follow-up was pointed to increase mortality in SLE patients. The higher SLICC damage index was shown to be a predictor of mortality in various studies in different SLE patients [1]. Also, Telles et al. results are in accordance to ours. They showed that SAPS and SLICC damage index are risk factors for mortality [5].

A change towards cardiovascular disease as the main cause of death in SLE patients, similar to that found in developed countries like France [20], USA [11], UK [21], Denmark [22], and Norway [16]. But infection still remains an important cause of death in SLE patients in world [3, 19] and in Brazil as noticed by Souza et al. [23]. In our study, infection, SLE activity, and cardiovascular disease were the main known causes of death in accordance with the trend.

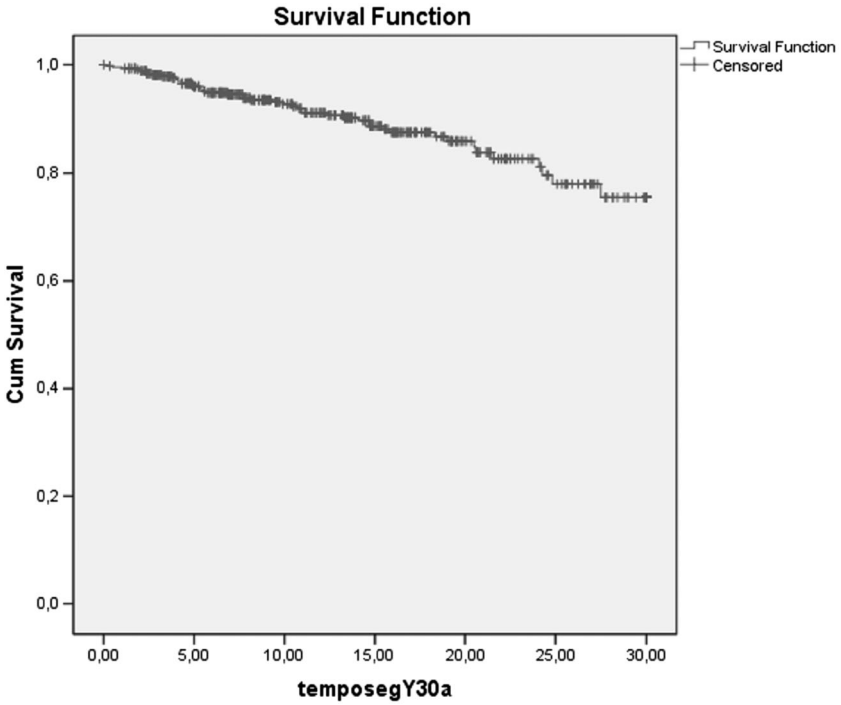

Fig. 1 Kaplan–Meier curve for survival in SLE patients

Yurkovich's et al. [24] meta-analysis included 12 studies about SLE mortality. Cardiovascular disease and infection were identified as the main causes of death. They also showed a higher mortality risk in patients with renal disease and an increased risk of death from malignancy in SLE population. The former were not considered as a direct cause of death in our study but we identified three (6%) attributed to malignancy. Malignancy was the second cause of death in the UK after cardiovascular disease [21]. A recent meta-analysis showed an increased mortality from cardiovascular disease and infection but cancer-related mortality was not elevated for SLE patients than in general population [25].

A significant result from our study is the important protection factor of antimalarial use for mortality. This were also seen by Ruiz-Irastorza et al. [26], Alarcón et al. [27], Shinjo et al. [28].

One of the limitations of this study is the high prevalence of unknown cause of death was attributed to the poor official records in our country so patients who were not assisted in our hospital at the time of death had bad official registries.

Table 2 Cox regression models for 30-year survival rate in systemic lupus erythematosus

Variables	Univariate Analysis[a] HR (CI 95%)	Multivariate Analysis[b] HR (CI 95%)
European-derived	0.505 (0.278–0.918)	
Sex (female)	0.533 (0.226–1.258)	
Age at diagnosis	1.049 (1.027–1.070)	1.065 (1.039–1.092)
SLICC damage index	1.220 (1.050–1.417)	1.299 (1.076–1.569)
Anti-dsDNA	0.511 (0.277–0.945)	
Arthritis	0.549 (0.288–1.050)	
Cardiovascular disease	2.651 (1.442–4.874)	
Hypertension	2.254 (1.117–4.551)	
Diabetes	2.978 (1.472–6.024)	
Antiphospholipid syndrome	2.986 (1.384–6.443)	3.021 (1.307–6.985)
Methylprednisolone pulse therapy	1.837 (1.024–3.295)	2.628 (1.283–5.383)
Antimalarials	0.288 (0.103–0.804)	0.191 (0.064–0.570)

[a] Were listed the variables with p value <0.2

[b] Adjusted to variables with p value <0.2 in the univariate analyses besides age. The variables who had a p value <0.01 in the multivariate analyses were considered significant

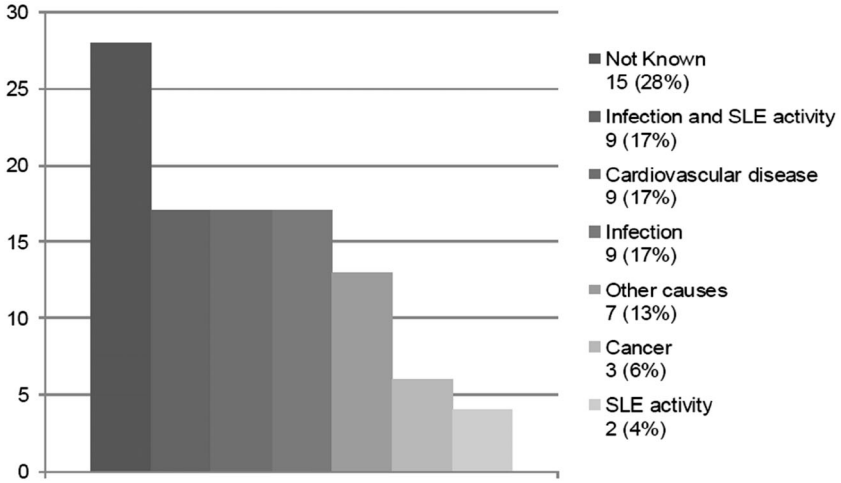

Fig. 2 Causes of death in SLE patients

Telles et al. also had unidentified cause of death in their analysis [5]. We tried to minimize this by calling patients' relatives but a lot of them were not found.

Conclusion

In conclusion, the main causes of death in our population were infection, SLE activity, and cardiovascular disease. The risk factors identified for worse survival were SAPS, highest SLICC index damage, advanced age at diagnosis, and high dose of corticosteroids. We could also corroborate that the use of antimalarials is effective on the prevention of death.

Compliance with ethical standards The study protocol was approved by local Ethics Committee and informed consent form was obtained from all participants at the beginning of the study or at the inclusion of new participants.

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