Mortality Profile Related to Systemic Lupus Erythematosus: A Multiple Cause-of-death Analysis

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ABSTRACT. ***Objective.*** To analyze the mortality profile related to systemic lupus erythematosus (SLE) in the state of São Paulo, Brazil.

Methods. For the 1985-2007 period, we analyzed all death certificates (n = 4815) on which SLE was listed as an underlying (n = 3133) or non-underlying (n = 1682) cause of death. We evaluated sex, age, and the causes of death, comparing the first and last 5 years of the period, as well as determining the observed/expected death ratio (O/E ratio).

Results. For SLE as an underlying cause, the mean age at death was 35.77 years (SD 15.12) and the main non-underlying causes of death were renal failure, circulatory system diseases, pneumonia, and septicemia. Over the period, the proportional mention of infectious causes and circulatory system diseases increased, whereas renal diseases decreased. For SLE as a non-underlying cause of death, the most common underlying causes of death were circulatory, respiratory, genitourinary, and digestive system diseases, and certain infections. The overall death O/E ratio was > 1 for renal failure, tuberculosis, septicemia, pneumonia, and digestive system diseases, as well as for circulatory system diseases at < 50 years of age, particularly acute myocardial infarct.

Conclusion. Unlike in developed countries, renal failure and infectious diseases are still the most frequent causes of death. The increase in SLE deaths associated with infection, especially pneumonia and septicemia, is worrisome. The judicious use of immunosuppressive therapy together with vigorous treatment of cardiovascular comorbidities is crucial to the successful management of SLE and to improving survival of patients with SLE. (First Release Jan 15 2012; J Rheumatol 2012;39:496–503; doi:10.3899/jrheum.110241)

Key Indexing Terms:
MULTIFACTORIAL CAUSALITY CAUSES OF DEATH SLE MORTALITY TRENDS
MORTALITY SYSTEMIC LUPUS ERYTHEMATOSUS VITAL STATISTICS

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that may affect any organ or system, presenting a wide array of clinical and laboratory manifestations that result in varying degrees of severity. Five-year survival in patients with SLE was about 50% in the 1950s. It has now increased to over 90%[1,2]. Nevertheless, mortality is still a concern, because the standardized mortality ratio for SLE may be as high as 4.6[3,4]. Deaths among patients with SLE can be caused by acute exacerbations, organ failure resulting from active disease, treatment, longterm complications of SLE, and other diseases unrelated to SLE. The prognosis is related to the pattern of organ involvement and the presence of comorbidities[5,6,7,8].

Knowledge of the causes of death and the related comorbidities is needed in order to improve strategies to prevent death in patients with SLE. One way of assessing mortality, in countries where accurate vital statistics are available, is to collect data from death certificates (DC). This represents the only affordable source of data that is consistently available at the national level, has broad coverage, and presents continuity[9].

Multiple cause-of-death analysis provides information regarding all conditions and circumstances involved in the process that culminated in a death, giving new perspectives on prevention[10]. It is particularly useful in the study of chronic diseases such as rheumatic disorders[11,12]. To our knowledge, to date there are no studies employing multiple cause-of-death analysis in SLE. In addition, data comparing mortality in patients with SLE with mortality observed in the general population are scarce in developing countries.

The aim of our study was to evaluate the mortality profile of SLE in the state of São Paulo, Brazil, using multiple cause-of-death analysis.

MATERIALS AND METHODS

Region of interest. The state of São Paulo is one of the most populous areas in Latin America, with over 40 million inhabitants; it is located in the southeastern region of Brazil. It is also the richest state in Brazil, account-

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ing for > 31% of the gross national product[13]. In the state of São Paulo there is only 1 previous study that has analyzed the trends in SLE mortality rates[14].

Data source. We obtained data regarding SLE-related deaths that occurred from 1985 to 2007 from the São Paulo State Data Analysis System Foundation (Fundação Sistema Estadual de Análise de Dados, http://seade.gov.br), which is responsible for the maintenance of vital statistics records. Population data for the same period were obtained from the Information Technology Department of the Brazilian Unified Health Care System (www.datasus.gov.br, an organ of the Brazilian National Ministry of Health, Office of the Executive Secretary).

Death registration. In Brazil, the official reporting of deaths is mandatory[15]. The DC is the official document, and the data obtained from this document are entered into a national database[16].

The medical certification portion of the DC used in Brazil follows the format of the World Health Organization (WHO) International Form of Medical Certificate of Cause of Death. According to WHO, underlying cause of death is defined as (1) the disease or injury which initiated the train of morbid events leading directly to death; or (2) the circumstances of the accident or violence which produced the fatal injury[17], and the contributing cause of death is defined as other significant conditions contributing to the death but not related to the disease or condition causing it. Complications of the underlying cause and the contributing causes are collectively designated the non-underlying causes of death. The term "multiple causes of death" refers to the sum of all causes (underlying and non-underlying).

In São Paulo, the State Bureau of Vital Statistics receives a copy of all DC, processes the demographic data, assigns a code to each cause of death in accord with the most recent revision of the International Classification of Diseases (ICD), selects the underlying cause of death according to the accepted international rules, and sends the data to the National Ministry of Health.

Identification of SLE-related deaths. We analyzed each DC listing a diagnosis of SLE on any line of the medical certification. For the 1985-1995 period we looked for subcategory 710.0, as SLE was coded in the ICD-9[18]. For the 1996-2007 period, we looked for category M32 and its subcategories (M32.1, M32.8, and M32.9), as SLE was coded in the ICD-10[19].

Multiple cause-of-death analysis. For each DC listing SLE as an underlying cause of death, the non-underlying causes were investigated, and for each DC where SLE was listed as a non-underlying cause of death, the underlying cause of death was examined. The expression "mortality related to" refers to the listing of a given condition either as the underlying or as a non-underlying cause, and the expression "proportional mortality from" refers to the percentage of the total number of deaths in which a given condition was the underlying cause of death.

We compared underlying and non-underlying causes of death between the first 5 years (1985-1989) and the last 5 (2003-2007). We calculated age-and sex-adjusted ratios of the number of observed deaths to the number of expected deaths for each cause (O/E ratio). The number of expected deaths was based on the proportional mortality in the general population by the same cause. In order to examine the non-underlying causes of death, we compiled a list of causes of death related to the natural history of SLE according to the literature[4,20,21,22,23] and causes of special interest in our country.

In order to establish equivalence between the ICD-9 and ICD-10 codes, we used the WHO bridge coding[24]. To process the medical variables, we used the programs dBASE III Plus, version 1.1, and Epi Info, version 6.04d, together with Microsoft Excel 2002. To tabulate the non-underlying causes of death and the mean number of causes of death per DC, we used the Tabulador de Causas Múltiplas [TCM, Multiple Causes (of death) Tabulator] program for ICD-9 and ICD-10 (TCM-9, version 4.0; and TCM-10, version 2.2, respectively)[25].

Demographic variables. We evaluated the variables for sex, age, and mean age at death. To process the demographic variables, we used the Epi Info program, version 6.04d, and Microsoft Excel 2002.

Statistical analysis. We present categorical variables as absolute values and percentages and continuous variables as means and SD. To compare the proportional mention of non-underlying causes of death among different age brackets and the proportional mention of non-underlying causes between 2 periods, as well as to calculate the O/E ratio for SLE, we used the chi-square test. For comparison of the mean age at death between 2 periods we used Student's t tests. In all statistical analyses, we employed the Minitab package and the Statistical Package for the Social Sciences, version 13.0. We set the level of significance at $p < 0.05$.

RESULTS

Among the DC issued in the state of São Paulo between 1985 and 2007, SLE was mentioned on 4815 (as the underlying cause of death on 3133 and as a non-underlying cause of death on 1682). The female/male ratio was 9:1 and remained stable throughout the period.

SLE as underlying cause of death. For the deaths in which SLE was listed as the underlying cause of death, the mean (SD) age at death (1985-2007) was 35.8 (15.12) years, without significant difference between the sexes. The mean (SD) age at death was higher over the last 5 years than over the first 5 years [38.5 (15.81) vs 32.9 (13.47) years, respectively; $p < 0.001$].

Table 1 shows the non-underlying causes of death by period. The main non-underlying causes of death were renal failure, circulatory system diseases, pneumonia, and septicemia. There were no significant differences between the sexes (data not shown).

Table 2 shows the non-underlying causes of death by age bracket at death. Diseases of the circulatory system and infections were more often mentioned for deaths occurring at age ≥ 50 years ($p < 0.001$). Hypertensive diseases, cerebrovascular diseases, and heart failure were the most common circulatory system diseases in all age groups. The percentages of acute nephritic syndrome/nephrotic syndrome/hematuria were lower in deaths at younger ages than in deaths at older ages ($p < 0.001$).

Of the 3133 deaths due to SLE as underlying cause, 536 (17.1%) had undergone autopsy. In those cases the most common non-underlying causes of death were similar to those reported for all SLE deaths.

SLE as non-underlying cause of death. Table 3 shows the underlying causes of death listed when SLE was mentioned as a non-underlying cause of death, by period. In this group the mean (SD) age at death was 40.8 (16.10) years, and the main underlying causes of death were in the circulatory, respiratory, digestive, and genitourinary systems, and certain infectious diseases. Neoplasms were listed as underlying causes of death in 93 (5.5%) of all DC. The most common neoplasms were malignant neoplasms of lymphoid, hematopoietic, and related tissue, which accounted for 19 (20%). Among them, 11 (58%) were attributed to leukemia and 5 (26%) to non-Hodgkin's lymphoma (NHL). The highest O/E ratio for specific neoplasm was 2.2 for malignant neoplasm of the ovary; whereas the O/E for NHL was 1.1, and for leukemia 1.3.

Table 1. Non-underlying causes of death when systemic lupus erythematosus was the underlying cause, by period, age-adjusted, state of São Paulo, Brazil. From São Paulo State Data Analysis System Foundation (Fundação Sistema Estadual de Análise de Dados, http://www.seade.gov.br); with permission.

Non-underlying Causes of Death	Coding ICD-9/ICD-10	1985–2007, n (%)	1985–1989, % (95% CI)	2003–2007, % (95% CI)	p
Renal failure	584.5–586/N17–N19	932 (29.8)	36.5 (31.10–42.96)	26.5 (23.01–30.34)	< 0.001
Pneumonia due to bacteria and other infectious organisms	481.0–483.0/485.0–486.0 J13.0–J16.8/J18.0–J18.9	805 (25.7)	15.6 (12.25–20.00)	31.8 (28.10–35.97)	< 0.001
Septicemia	038.0–038.9/A40.0–A41.9	714 (22.8)	12.0 (8.96–16.17)	33.4 (29.91–38.07)	< 0.001
Cerebrovascular diseases	430.0–432.9/I60.0–I62.9 434.9/I63.0–I63.9 436.0/I64.0	186 (5.9)	6.4 (4.27–6.75)	4.5 (3.17–6.30)	0.159
Heart failure	428.0–428.9/I50.0–I50.9	176 (5.6)	6.6 (4.39–10.01)	5.0 (3.36–6.82)	0.240
Acute nephritic syndrome/ nephrotic syndrome/ hematuria	580.0–581.3/581.9–582.4 582.9–583.9/N00.0–N06.9	150 (4.8)	5.6 (3.65–8.71)	1.8 (0.99–2.99)	0.001
Hypertensive diseases	401.0–404.9/I10.0–I13.9	245 (7.8)	5.1 (3.15–8.25)	10.6 (8.54–13.11)	< 0.001
Intracerebral hemorrhage	430.0–432.9/I60.0–I62.9	105 (3.4)	4.2 (2.52–7.06)	3.6 (2.41–5.26)	0.502
Gastrointestinal hemorrhage	578.0–578.9/K92.0–K92.2	49 (1.6)	1.6 (1.62–0.69)	1.0 (0.45–2.01)	0.298
Stroke, not specified as hemorrhage or infarction	436.0/I64.0	52 (1.7)	1.5 (0.53–3.98)	0.8 (0.32–1.75)	0.331
Malignant neoplasms	140.0–199.1/C00.0–C80.9	21 (0.7)	0.4 (0.05–2.41)	0.3 (0.06–1.01)	1.000
Cerebral infarction	434.9/I63.0–I63.9	29 (0.9)	0.7 (0.19–2.75)	0.1 (0.00–0.78)	0.142
Acute myocardial infarction	410.0/I21.0–I21.9	57 (1.8)	0.9 (0.30–3.02)	3.0 (2.00–4.51)	0.051
Disseminated intravascular coagulation	286.6/D65.0	40 (1.3)	0.6 (0.12–2.58)	2.1 (1.20–3.50)	0.062
Encephalitis	323.8–323.9/G04.8–G04.9	15 (0.5)	0.7 (0.15–2.88)	0.7 (0.21–1.60)	1.000
Meningitis	322.0–322.9/G03.0 G03.8–G03.9	9 (0.3)	0.9 (0.13–3.30)	0.3 (0.03–1.08)	0.268
Tuberculosis	010.0–018.9/A15.0–A19.9	19 (0.6)	0.3 (0.04–2.29)	0.4 (0.08–1.20)	1.000
Total deaths		3133	489	846	

ICD: International Classification of Diseases.

As shown in Table 4, we found an O/E ratio > 1 for renal failure, tuberculosis, septicemia, pneumonia, and digestive system diseases. The O/E ratio for renal failure was higher in the 1996-2000 period than in 2003-2007. Considering only the SLE deaths occurring at age < 50 years, we found an O/E ratio > 1 for diseases of the circulatory system, specifically cerebrovascular diseases and acute myocardial infarction (AMI; Table 5). However, when we analyzed death at age > 50 years, the O/E ratios for circulatory system (OR 0.32, 95% CI 0.27–0.38, p = 0.001), specifically cerebrovascular diseases (OR 0.29, 95% CI 0.20–0.40, p = 0.001) and AMI (OR 0.36, 95% CI 0.26–0.49, p = 0.001), were < 1 for the whole period.

DISCUSSION

To our knowledge, this is the first study in the literature using multiple cause-of-death analysis in SLE. In the state of São Paulo there is total coverage of all deaths[26]. The quality of the available vital statistics facilitated our study. The mean number of diagnoses per DC (3.78) was well above the minimum of 2.6 stipulated by the Pan American Health Organization for multiple cause-of-death analyses[27]. The use of multiple cause-of-death analysis allowed us to identify a greater number of SLE-related deaths, 35% of which would otherwise have been overlooked.

In our study, for all SLE-related deaths, the mean age at death was lower than reported in many international studies[28,29]. The most common non-underlying cause of death was renal failure. Renal failure as a non-underlying cause of death had high prevalence in adults as in younger individuals. The O/E of 5.59 showed patients with SLE died much more often due to renal failure than did the general population. Although earlier studies of SLE-related deaths also reported high proportions of renal failure as a cause of death[5,30,31], more recent studies in developed countries have indicated lower prevalence of renal failure as a cause of death in SLE[4,21,32].

Comparing the 1985-1989 period with the 2003-2007 period, we found a decline not only in the proportion of renal failure mentioned as a non-underlying cause of death, but also in the O/E ratio for renal failure as the underlying cause of death. These changes are likely attributable to recent improvements in the management of renal disease.

Since 1976, when Urowitz, *et al* reported the bimodal pattern of mortality[33], many studies have shown that atherosclerotic cardiovascular diseases are frequent causes of

Table 2. Non-underlying causes of death when systemic lupus erythematosus was the underlying cause, by age bracket, state of São Paulo, Brazil, 1985–2007. From São Paulo State Data Analysis System Foundation (Fundação Sistema Estadual de Análise de Dados, http://www.seade.gov.br); with permission.

Non-underlying Causes of Death	Coding ICD-9/ICD-10	Age, yrs < 20, n (%)	20–49, n (%)	≥ 50, n (%)	p
Renal failure	584.5–586/N17–N19	124 (28.19) (a,b)	669 (31.77) (a)	139 (23.68) (b)	< 0.001
Pneumonia due to bacteria and other infectious organisms	481.0–483.0/J13.0–J16.8 485.0–486.0/J18.0–J18.9	98 (22.28) (a)	534 (25.36) (a,b)	173 (29.47) (b)	0.027
Diseases of the circulatory system	401.0–404.9/I10.0–I13.9 410.0/I21.0–I21.9 411.0–412.0; 414.0–414.9/I22.0–I25.9 415.1/I26.0–I26.9 416.0/I27.0 428.0–428.9/I50.0–I50.9 430.0–432.9/I60.0–I62.9 434.9/I63.0–I63.9 436.0/I64.0	72 (16.36) (a)	552 (26.21) (b)	179 (30.49) (c)	< 0.001
Septicemia	038.0–038.9/A40.0–A41.9	100 (22.73)	474 (22.51)	140 (23.85)	0.729
Hypertensive diseases	401.0–404.9/I10.0–I13.9	15 (3.41) (a)	174 (8.26) (b)	56 (9.54) (b)	0.001
Cerebrovascular diseases	430.0–432.9/I60.0–I62.9 434.9/I63.0–I63.9 436.0/I64.0	30 (6.82)	128 (6.07)	28 (4.77)	0.492
Heart failure	428.0–428.9/I50.0–I50.9	16 (3.64) (a)	115 (5.46) (a, b)	45 (7.67) (b)	0.018
Acute nephritic syndrome/ nephrotic syndrome/ hematuria	580.0–581.3/581.9–582.4 582.9–583.9/N00.0–N06.9	37 (8.41) (a)	98 (4.65) (b)	15 (2.55) (c)	< 0.001
Intracerebral hemorrhage	430.0–432.9/I60.0–I62.9	19 (4.32) (a, b)	76 (3.61) (a)	10 (1.70) (b)	0.033
Pulmonary embolism	415.1/I26.0–I26.9	9 (2.04)	62 (2.94)	20 (3.41)	0.430
Acute myocardial infarction	410.0/I21.0–I21.9	0 (0.00) (a)	39 (1.85) (b)	18 (3.07) (b)	0.001
Stroke, not specified as hemorrhage or infarction	436.0/I64.0	6 (1.36)	32 (1.52)	14 (2.38)	0.304
Gastrointestinal hemorrhage	578.0–578.9/K92.0–K92.2	5 (1.14) (a, b)	26 (1.23) (a)	18 (3.07) (b)	0.005
Disseminated intravascular coagulation	286.6/D65.0	9 (2.04) (a)	29 (1.37) (a)	2 (0.34) (b)	0.043
Other ischemic heart diseases	411.0–412.0 414.0–414.9/I22.0–I25.9	0 (0.00) (a)	11 (0.5) (a)	10 (1.70) (b)	0.001
Cerebral infarction	434.9/I63.0–I63.9	5 (1.14)	20 (0.95)	4 (0.68)	0.738
Primary pulmonary hypertension	416.0/I27.0	2 (0.45)	21 (1.00)	2 (0.34)	0.196
Malignant neoplasms	140.0–199.1/C00.0–C80.9	0 (0.00)	15 (0.71)	6 (1.02)	0.128
Tuberculosis	010.0–018.9/A15.0–A19.9	0 (0.00)	15 (0.71)	4 (0.68)	0.209
Encephalitis	323.8–323.9/G04.8–G04.9	0 (0.00)	15 (0.71)	4 (0.68)	0.209
Meningitis	322.0–322.9/G03.0 G03.8–G03.9	3 (0.68)	5 (0.24)	1 (0.17)	0.240
Total deaths		440	2.106	587	

a, b, c: Percentages that have letters in common have no statistically significant difference. Percentages that have different letters have statistically significant difference only between themselves. ICD: International Classification of Diseases.

death in SLE[4,21,34,35,36]. In accord with these studies, we observed that diseases of the circulatory system constituted the second leading non-underlying cause of death, and they had increased recently due to an increase in the frequency of AMI and hypertensive diseases.

Among the underlying causes of death, diseases of the circulatory system constituted the main cause, and this remained unchanged throughout the study period. The O/E ratio for diseases of the circulatory system and specifically AMI in all age brackets was < 1. This means that deaths due to diseases of the circulatory system are less common in patients with SLE than in the general population.

None the less, the literature shows that patients with SLE are at a higher risk of developing an atherosclerotic cardiovascular disease, particularly at an early age[37,38]. Our study also found an O/E ratio > 1 for mortality due to circulatory system diseases as well as cerebrovascular diseases specifically, in deaths at age < 50 years.

We found that the O/E ratio for mortality due to AMI at

Table 3. Underlying causes of death when systemic lupus erythematosus was the non-underlying cause, by period, standardized, age-adjusted, state of São Paulo, Brazil. From São Paulo State Data Analysis System Foundation/Information Technology Department of the Brazilian Unified Health Care System (Fundação Sistema Estadual de Análise de Dados, http://www.seade.gov.br); with permission.

Underlying Causes of Death	Coding ICD-9/ICD-10	1985–2007, n (%)	1985–1989, % (95% CI)	2003–2007, % (95% CI)	p
Certain infectious and parasitic diseases	001–139/A00–B99	203 (12.07)	13.7 (8.97–21.35)	14.0 (10.83–18.05)	0.933
Tuberculosis	010–018/A15–A19	47 (2.79)	3.3 (1.20–8.88)	2.4 (1.15–4.42)	0.523
Septicemia	038.9–0.36.2/A40–41	65 (3.86)	4.8 (2.32–10.47)	4.5 (2.81–7.00)	0.877
Mycoses	110–118/B35–B49	16 (0.95)	2.0 (0.52–7.20)	1.0 (0.26–2.64)	0.279
Neoplasms	140–239/C00–D48	93 (5.52)	4.5 (1.73–10.74)	5.9 (4.13–8.48)	0.492
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	280–289/D50–D89	88 (5.23)	3.0 (1.17–8.25)	4.7 (2.92–7.27)	0.214
Disseminated intravascular coagulation	286.6/D65	9 (0.53)	0.8 (0.09–5.42)	0.7 (0.14–2.21)	0.791
Immunodeficiency, unspecified	279.3/D84.9	47 (2.79)	3.4 (1.35–8.90)	4.3 (2.59–6.86)	0.521
Endocrine, nutritional and metabolic diseases	240–278/E00–E90	61 (3.63)	6.8 (3.65–12.96)	8.0 (5.70–10.99)	0.506
Diseases of the nervous system	320–359/G00–G99	35 (2.08)	3.2 (1.37–8.38)	1.1 (0.34–2.74)	0.094
Diseases of the circulatory system	390–444 447–459/I00–I99	462 (27.46)	28.8 (21.45–38.78)	29.2 (24.72–34.34)	0.862
Hypertensive diseases	401–405/I10–I15	36 (2.14)	3.0 (1.29–8.05)	2.0 (1.03–3.87)	0.541
Hypertensive renal disease	403/I12	89 (5.29)	1.7 (0.56–6.50)	0.4 (0.04–1.66)	0.057
Ischemic heart diseases	410–414/I20–I25	41 (2.44)	6.3 (2.99–12.82)	6.2 (4.34–8.81)	0.996
Acute myocardial infarction	410/I21.0–I21.9	22 (1.31)	5.6 (2.55–12.00)	4.4 (2.88–6.76)	0.441
Pulmonary heart disease and diseases of pulmonary circulation	415–417/I26–I28	108 (6.42)	2.90 (1.00–8.25)	2.22 (1.13–4.14)	0.643
Pulmonary embolism	415.1/I26	37 (2.20)	2.5 (0.74–7.75)	1.0 (0.38–2.59)	0.155
Cerebrovascular diseases	430–438/I60–I69	309 (18.37)	9.6 (5.48–16.78)	6.8 (4.75–9.70)	0.226
Stroke, not specified as hemorrhage or infarction	436/I64	8 (0.47)	3.4 (1.09–9.16)	0.7 (0.18–2.07)	0.051
Diseases of arteries, arterioles, and capillaries	440–448/I70–I79	170 (10.11)	0.3 (0.01–4.93)	2.8 (1.55–4.94)	0.051
Diseases of the respiratory system	460–519/J00–J99	156 (9.27)	22.5 (16.22–31.54)	11.3 (8.65–14.70)	< 0.001
Bacterial pneumonia, not elsewhere classified	482/J15	32 (1.90)	0.1 (0.00–4.68)	0.4 (0.09–1.72)	1.000
Pneumonia, organism unspecified	485–486/J18	28 (1.67)	11.6 (7.06–19.14)	4.6 (2.91–7.08)	0.005
Diseases of the digestive system	520–579/K00–K93	156 (9.27)	7.5 (4.00–14.13)	9.5 (6.97–12.70)	0.386
Diseases of the skin and substaneous tissue	680–709/L00–L99	16 (0.95)	0.4 (0.01–4.99)	1.9 (0.90–3.79)	0.195
Diseases of the musculoskeletal and connective tissue	710–739/446 M00–M99	80 (4.76)	1.0 (0.02–6.26)	1.9 (0.94–3.72)	0.525
Diseases of the genitourinary system	580–629/N00–N99	18 (1.07)	8.1 (4.78–14.42)	8.2 (5.79–11.31)	0.948
Acute renal failure	584/N17	14 (0.83)	0.8 (0.10–5.48)	0.6 (0.13–2.19)	0.625
Chronic renal failure	585/N18	16 (0.96)	4.41 (2.03–9.99)	2.73 (1.43–4.89)	0.347
Unspecified renal failure	586/N19	2 (0.12)	1.9 (0.61–6.84)	0.3 (0.04–1.56)	0.057

ICD: International Classification of Diseases.

age < 50 years was 2.2, showing that, in the state of São Paulo, premature death due to AMI was higher in patients with SLE than in the general population. These findings indicate that cardiovascular events occur not only in older patients with longstanding disease, but also in younger patients who are at higher cardiovascular risk.

One possible explanation for O/E ratios < 1 for diseases of the circulatory system for all age brackets is that a small number of SLE deaths occurred at age ≥ 50 years.

Doria[39] makes important comments about the high number of variables implicated in accelerated atherosclerosis in patients with SLE. An interesting aspect is the cutoff dosage of corticosteroids that would balance favorable and adverse effects related to accelerated atherosclerosis. Another

Table 4. Observed/expected ratios for underlying causes of death in systemic lupus erythematosus, in all ages, by period, state of São Paulo, Brazil. Data are OR (95% CI) and p value. From São Paulo State Data Analysis System Foundation/Information Technology of the Brazilian Unified Health Care System (Fundação Sistema Estadual de Análise de Dados, http://www.seade.gov.br); with permission.

Cause of Death	1985–2007	1985–1989	2003–2007
Renal failure	5.59 (4.27–7.20)*	8.64 (6.02–12.03)**	3.78 (2.27–5.92)
p	0.001	0.001	0.001
Tuberculosis	4.86 (3.57–6.46)	5.65 (2.24–11.70)	5.00 (2.48–8.98)
p	0.001	0.001	0.001
Septicemia	4.48 (46–5.72)	5.37 (2.66–9.63)	5.13 (3.25–7.71)
p	0.001	0.001	0.001
Pneumonia	1.91 (1.64–2.22)	1.94 (1.26–2.87)	0.90 (0.59–1.31)
p	0.001	0.001	0.257
Disease of the digestive system	1.75 (1.48–2.04)	1.36 (0.74–2.28)	1.64 (1.22–2.15)
p	0.001	0.243	0.004
Hypertensive diseases	1.02 (0.72–1.42)	1.92 (0.82–3.80)	0.69 (0.33–1.27)
p	0.881	0.059	0.122
Diseases of the circulatory system	0.88 (0.80–0.96)	0.82 (0.62–1.06)	1.00 (0.86–1.17)
p	0.001	0.063	0.111
Cerebrovascular diseases	0.71 (0.58–0.85)	0.81 (0.47–1.30)	0.81 (0.57–1.12)
p	0.001	0.34	0.052
Acute myocardial infarction	0.51 (0.40–0.66)	0.57 (0.26–1.08)	0.66 (0.43–0.97)
p	0.001	0.071	0.005
Neoplasms	0.39 (0.32–0.48)	0.29 (0.11–0.60)	0.39 (0.27–0.55)
p	0.001	0.005	0.001

* 1996–2007 period. ** 1996–2000 period.

Table 5. Observed/expected ratios for underlying causes of death in systemic lupus erythematosus, age < 50 years, by period, state of São Paulo, Brazil. Data are OR (95% CI) and p value. From São Paulo State Data Analysis System Foundation and Information Technology Department of the Brazilian Unified Health Care System (Fundação Sistema Estadual de Análise de Dados, http://www.seade.gov.br); with permission.

Cause of Death	1985–2007	1985–1989	2003–2007
Diseases of the circulatory system	4.75 (4.24–5.31)	4.37 (3.18–5.88)	5.63 (4.56–6.87)
p	0.001	0.001	0.001
Cerebrovascular diseases	3.35 (2.61–4.23)	4.17 (2.27–7.01)	4.22 (2.61–6.46)
p	0.001	0.001	0.001
Acute myocardial infarction	2.20 (1.57–3.01)	2.38 (0.86–5.22)	3.22 (1.80–5.32)
p	0.001	0.116	0.001

important aspect of successful treatment of SLE is early diagnosis[40].

Infection was a leading non-underlying cause of death, as reported[20,31,33], and the recent increases are cause for concern. The O/E > 1 for septicemia and pneumonia remained over the study period, showing the deaths in patients with SLE due to infection now are still higher than in the general population.

Although we did not find tuberculosis to be a common non-underlying cause of death, the mortality due to tuberculosis was higher in patients with SLE than in the general population.

Various authors have reported that patients with SLE are at an increased risk of death from malignant lymphoid and hematopoietic neoplasms, especially NHL, lung cancer, and breast cancer[4,41,42]. We did not find neoplasm to be a leading non-underlying cause of death. In addition, the O/E ratio for mortality due to neoplasia was < 1, indicating that, in the state of São Paulo, proportional mortality due to neoplasia is lower in patients with SLE than in the general population. This finding is probably attributable to the premature mortality observed in our study, since cancer typically develops in older age.

Some authors suggest that immunosuppressive therapy is also associated with a greater risk of malignancy[42]. However, 1 study reported that the relative risk of cancer is highest in the early years after the diagnosis of SLE[43], suggesting that the cumulative effects of immunosuppressive

therapy do not increase the risk of cancer. The effects that drug exposure and disease activity have on the risk of cancer in patients with SLE remains unclear[44].

In our study, the type of neoplasia most often found as an underlying cause of death was neoplasm of the lymphoid, hematopoietic, or related tissue. However, the highest O/E ratio for mortality due to malignant neoplasm was for ovarian neoplasm.

Our study has certain limitations that are inherent to the approach taken. Principally, DC can present inaccuracies resulting from diagnostic errors, a lack of medical records at the time of certification (mainly in SLE patients with longstanding and inactive disease), poor physician training in filling out DC, and errors at the stage of ICD coding of the causes of death. This is similar to what occurs in other countries[11].

One strength of our study is that we included all SLE-related deaths and therefore varying degrees of SLE severity, which is quite important in the overall analysis of causes of death. Further, the extensive coverage of deaths in the state of São Paulo and the continuity of the data analyzed allowed the analysis of longterm mortality profiles and made it possible to detect changes in the distribution of causes of death in SLE. These changes in the causes of death are consistent with recent increases in the longevity of patients with SLE in São Paulo.

However, the recent increase in mortality associated with infections, especially pneumonia and septicemia, is worrisome. The increase is probably attributable to the fact that immunosuppressive therapy has recently come to be used more aggressively. Although this strategy provides better control of renal disease, it increases the risk of severe infections. The judicious use of immunosuppressive therapy together with vigorous treatment of cardiovascular comorbidities is crucial to the successful management of SLE and to improving patient survival.

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