A Study of Multiple Causes of Death in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate rheumatoid arthritis (RA)–related mortality in the state of São Paulo (Brazil).
Methods. Data from all death certificates (DC) from 1996 to 2010 were analyzed using a multiple cause-of-death method. We compared the results from 2 subperiods (1996-2000 and 2006-2010).
Results. We found 3955 DC related to RA — 27.6% with RA as the underlying cause of death (UCD) and 72.4% with RA as the nonunderlying cause of death (NUCD). Ninety percent of RA-related deaths occurred at age ≥ 50 years. The mean ages at death were 67.1 ± 13.3 and 67.9 ± 13 years for RA as the UCD and NUCD, respectively. The most frequent NUCD associated with RA were pneumonia, sepsis, renal failure, interstitial lung disease, and heart failure. In the last subperiod, there was an increase in infectious causes. When RA was an NUCD, we observed a decrease in the mean age at death for the last subperiod ($p = 0.021$). The most common UCD were circulatory and respiratory system diseases. Comparing the mean age at death between RA-related deaths and the general population when deaths occurred at ages beyond 50 years, the linear regression analysis showed a downward curve for RA-related death ($p < 0.001$ and $r = –0.795$), while for the general population, as expected, the curve had an upward pattern ($p < 0.001$ and $r = 0.993$).
Conclusion. Unexpectedly, RA-related deaths occurred at earlier ages in the more recent subperiod. Cardiovascular disease remained the most important cause, and infectious diseases are an increasing cause of death associated with RA, raising the question of whether infections were related to the more vigorous immunosuppressive treatment recommended by recent guidelines. (J Rheumatol First Release October 15 2015; doi:10.3899/jrheum.150166)

Key Indexing Terms:
RHEUMATOID ARTHRITIS MORTALITY CAUSES OF DEATH
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Rheumatoid arthritis (RA) is the most common cause of chronic inflammatory arthritis and its prevalence is estimated at 0.5% to 1% of the adult population around the world[1,2]. In Brazil, there are no studies evaluating a representative sample of the whole population. Studies evaluating specific cities have shown a prevalence rate varying from 0.2 to 1%[3,4].

RA can affect persons at any age, and prevalence rises with aging; it is highest in women older than 65 years. The estimated prevalence varies geographically, with the highest rates in northern Europe and North America[1].

Despite the main clinical characteristic of articular involvement, other systems can be involved and are associated with worsening of life expectancy. Patients with RA have a higher frequency of comorbidities than those seen in the general population. These comorbidities are intrinsically related to higher levels of mortality. The standardized mortality ratio varies between 1.2 and 1.3 in inception cohorts and 1.6 and 1.7 in noninception cohorts[5].

One way to evaluate mortality is to use data listed on a death certificate (DC). Evaluation of DC data is low in cost, has broad coverage, and presents continuity[6]. In Brazil, copies of the DC are sent to the state bureaus of vital statistics or departments of epidemiological surveillance, where the demographic and medical data are encoded and processed. The resulting datasets are then forwarded to the Brazilian Ministry of Health for consolidation at the national level[7].

Despite the acknowledged value of the underlying cause of death (UCD) in studying and understanding the patterns of diseases, with the aging of the population, an increasing number of comorbidities related to the dead individual and valuable information are lost if only the UCD is considered. Deaths due to chronic pathologies such as rheumatic diseases are not well characterized by a single cause; rather, they are more likely to represent a number of coexisting conditions[8,9] that contribute to the outcome. The study of multiple causes of death adequately allows a complete understanding of the pathological events that culminated in death. In addition, it allows recognizing improbable or unknown associations.

The aim of our study was to evaluate RA-related mortality in São Paulo, the most populous state in Brazil.

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MATERIALS AND METHODS

Geographic and demographic information. The state of São Paulo is located in the southeast region of Brazil and has an area of 248,222.8 km^2, slightly smaller than the United Kingdom. In 2010 it had a population of 41,262,199, distributed in 645 municipalities[10]. São Paulo is the richest state of the federation and is responsible for 33.1% of the Brazilian gross domestic product[11].

Data source. We analyzed mortality data obtained from the São Paulo Data Analysis System Foundation (Fundação Sistema Estadual de Analise de Dados), the institution responsible for vital statistics in São Paulo.

In Brazil, the DC is established according to World Health Organization (WHO) recommendation and is composed of 2 parts: the first presents the sequence of events leading to death, with UCD stated on the last line, and the second part is composed of contributing causes of death. According to WHO, the UCD is defined as "(a) disease or injury which initiated the train of morbid events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury"[12]. All the causes of death written on the DC, with the exception of the UCD, were described as nonunderlying causes of death (NUCD). The term *multiple causes of death* refers to the set of all causes (underlying and nonunderlying).

We analyzed all DC data that had codes associated with RA, recognized as category M05 (seropositive RA) and subcategories M06.0 (seronegative RA), M06.1 (Still disease), M06.8 (other specified RA), and M06.9 (RA, unspecified) on any line of the DC, in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th Revision[12], in use in Brazil since 1996.

Mortality rates. We evaluated all DC data from 1996 to 2010 and calculated the crude annual mortality rate by age and sex, using demographic data provided by the Information Technology Department of The Brazilian Unified Health Care System (DATASUS; an organ of the Brazilian National Ministry of Health)[13].

The age and sex-adjusted mortality rate was calculated by the direct method over the entire period and annually, using the Brazilian population in 2000 as reference. All mortality rates were calculated per million inhabitants.

Multiple causes of death. For all analyses, except mortality rate, we selected only DC data in which age at death was ≥ 20 years, to exclude juvenile idiopathic arthritis (< 16 yrs old) and to compare the age intervals of the general population, divided into 5-year intervals (e.g., 15-19 yrs).

When RA was described as UCD, we evaluated NUCD data described on the DC, and conversely, when RA was described as NUCD, we evaluated UCD data; we also estimated the observed/expected ratio (O/E ratio). O/E ratio is the ratio for 1 specific UCD associated with RA (observed) and the expected for the same UCD in the general population, allowing an estimate of whether the specific UCD is more (O/E ratio > 1) or less (O/E ratio < 1) frequent in RA-related deaths. If O/E ratio is equal to 1, it suggests a pattern similar to the general population. The O/E ratio was adjusted for sex and age.

Although we could not evaluate the treatment of patients, we decided to compare 2 specific subperiods (subperiod I: 1996-2000, and subperiod II: 2006-2010), which represent distinct approaches regarding treatments. In subperiod I, there were no patients using tumor necrosis factor inhibitors in Brazil. Meanwhile, in subperiod II, the treatment became more aggressive, with the intention of better controlling the inflammatory process. At that time, biologic therapy was made available by the public health system.

Similarly to Santo, *et al*[7], we used the expressions "death from" or "death due to" to refer to the UCD, whereas "deaths with a mention of" and "mortality related to" refer to a specific condition that could be UCD or NUCD.

For each data entry (RA as UCD or NUCD), we studied the following variables: sex distribution, age at death, the total number of causes listed per DC, and all described causes of death.

A subgroup of 166 DC were for cases submitted to autopsy and we compared the causes of death in the subgroup submitted to autopsy with the whole group of DC.

Statistical analysis. We presented the categorical variables as absolute values and percentages. For inferential analysis, we performed chi-squared or Fisher's exact test, depending on the sample size.

For continuous variables, we described as means and SD, and for inferential analysis, we first used the Kolmogorov-Smirnov test for normality and then the Student t test or the Mann-Whitney U test, according to the normality of the variables.

We performed linear regression analysis to assess the trend of standardized mortality rates and mean age of death over the years.

The variables were processed using the following programs: dBASE IV Plus (Ashton-Tate Corp.), Tabulador de Causas Múltiplas (Multiple Causes Tabulator) program (DATASUS, Health Ministry, School of Public Health, Universidade de São Paulo), EpiInfo 7.0 (US Centers for Disease Control and Prevention), Excel 2013 (Microsoft Corp.), Minitab 17 (Minitab 17 Statistical Software) and SPSS version 20 (IBM SPSS Statistics for Windows). The accepted significance level was 5% ($p < 0.05$).

The local institutional ethics committee approved our study.

RESULTS

For the entire period (1996–2010), 3,629,559 death certificates were issued in São Paulo state. The term *RA* was listed in 3955 DC, with 1095 (27.6%) as UCD and 2860 (72.4%) as NUCD. In 17 DC, the age at death was younger than 20 years (4 as UCD and 13 as NUCD). The annual mean of deaths with any mention of RA was 263.6. The female/male ratio was 3.3 for RA as UCD and 3.2 as NUCD (Table 1).

Figure 1 shows the distribution of RA-related deaths according to age ranges. Death was more common in females, and 90% of RA-related deaths occurred at older than 50 years.

The adjusted mortality rate for the entire period was 6.5 deaths/million inhabitants (Table 1), with highest values for females. In linear regression analysis, we did not find any trend over the period for females ($p = 0.13$ and $R = –0.409$) and males ($p = 0.09$ and $R = –0.452$).

The mean number of causes of death per DC with any mention of RA was 4.2 ± 1.2 for the entire period. We observed an increase in the number of RA-related entries over the years (3.9 ± 1.1 vs 4.4 ± 1.2, $p < 0.001$ for subperiod I and II, respectively).

RA as UCD. The mean age at death when RA was the UCD was 67.1 ± 13.3 years for the entire period (67.6 ± 13.2 for female vs 65.4 ± 13.6 for male, $p = 0.021$). There was no difference between subperiods.

The most important NUCD associated with RA were pneumonia (38.8%), sepsis (29.7%), renal failure (11.4%), interstitial lung disease (10.91%), and heart failure (9.1%). On subperiod comparison, subperiod II showed an increase in infectious causes (pneumonia and sepsis) and surgical operation with implant of artificial internal device, and a reduction in heart failure and stroke (Table 2).

RA as NUCD. The mean age at death when RA was the NUCD was 67.9 ± 13 years for the entire period (68.3 ± 13.1 for females vs 66.5 ± 12.5 for males, $p = 0.001$). Comparing subperiods, we observed a decrease in the mean age at death for the latter subperiod (68.4 ± 12.9 vs 67.1 ± 13.2 yrs; $p = 0.021$).

Table 1. Absolute number of RA-related deaths and adjusted mortality rate in São Paulo state, Brazil, from 1996 to 2010.

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
All RA-related deaths, n	194	241	203	251	254	239	264	269	272	295	268	268	312	303	322	3955
RA listed as the UCD	61	67	50	59	59	57	58	65	56	66	85	97	93	113	109	1095
Men	17	19	13	11	12	12	14	18	14	15	26	17	19	22	23	252
Women	44	48	37	48	47	45	44	47	42	51	59	80	74	91	86	843
Ratio F:M	2.6	2.5	2.8	4.4	3.9	3.8	3.1	2.6	3.0	3.4	2.3	4.7	3.9	4.1	3.7	3.3
Age, yrs																
0–19	2	0	0	0	1	0	0	0	0	0	0	0	0	1	0	4
20–39	3	4	1	2	1	1	0	3	3	5	3	3	4	1	3	37
40–59	9	15	12	13	18	9	15	11	15	19	21	20	23	26	29	255
60–79	34	36	29	33	26	36	32	45	32	31	44	52	50	64	59	603
≥ 80	13	12	8	11	13	11	11	6	6	11	17	22	16	21	18	196
RA listed as NUCD	133	174	153	192	195	182	206	204	216	229	183	171	219	190	213	2860
Men	32	47	42	47	38	37	45	44	51	61	37	50	59	47	40	677
Women	101	127	111	145	157	145	161	160	165	168	146	121	160	143	173	2183
Ratio F:M	3.2	2.7	2.6	3.1	4.1	3.9	3.6	3.6	3.2	2.8	3.9	2.4	2.7	3.0	4.3	3.2
Age, yrs																
0–19	2	3	0	0	0	1	1	1	0	2	0	0	1	0	2	13
20–39	8	8	2	5	1	4	4	2	5	5	7	4	3	4	7	69
40–59	19	30	31	28	46	43	41	40	54	49	47	51	50	44	51	624
60–79	79	98	102	120	111	105	117	125	113	133	94	86	127	105	122	1637
≥ 80	25	35	18	39	37	29	43	36	44	40	35	30	38	37	31	517
Age-standardized mortality rate*																
All RA-related deaths	6.0	7.3	6.0	7.4	6.5	6.1	6.6	6.6	6.6	7.0	6.3	5.3	6.1	5.7	5.9	6.5
Men	3.1	4.1	3.3	3.6	2.6	2.6	3.1	3.2	3.3	3.7	3.1	2.7	3.1	2.7	2.4	3.1
Women	8.7	10.3	8.5	11.1	10.2	9.3	10.0	9.9	9.8	10.1	9.3	7.6	8.8	8.5	9.0	9.6

* Per million inhabitants. RA: rheumatoid arthritis; UCD: underlying cause of death; NUCD: nonunderlying cause of death.

The most common UCD were circulatory (35.1%) and respiratory system diseases (21.8%). Among the circulatory system diseases, there was a predominance of the following categories: ischemic heart diseases (11.5%), cerebrovascular diseases (5.5%), and hypertensive diseases (4.2%). Unspecified organism pneumonia was the main cause of death in respiratory system diseases (9.4%), followed by chronic lower respiratory diseases (6.4%) and other interstitial pulmonary diseases (2.4%).

In the last subperiod, there was an increase of neoplasm, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, diseases of the nervous system, other interstitial pulmonary diseases, diseases of the musculoskeletal system and connective tissue, and unspecified site urinary tract infection. We also observed a decrease in diseases of the respiratory system, unspecified cerebral infarction, and renal failure (Table 3).

The O/E ratio was higher than 1 for sepsis, systemic mycosis, Cushing syndrome, chronic obstructive pulmonary disease, pneumonia, decubitus ulcer, pyogenic arthritis, and renal failure during the entire period.

Despite O/E = 1 for tuberculosis, considering both sexes and the entire period, we observed O/E higher than 1 (2.16; 95% CI 1.25-3.71) for women, without differences between subperiods. Table 4 shows the O/E ratio for the entire period and for subperiods.

We compared the mean age at death between RA-related deaths and in the general population, considering only deaths at age ≥ 50 years. Linear regression analysis showed a downward curve for RA-related deaths ($p < 0.001$ and $r = –0.795$) while for the general population, as expected, there was an upward pattern ($p < 0.001$ and $R = 0.993$; Figure 2).

Concerning the subgroup submitted to autopsy, we found 65 DC considering RA as a UCD, and in this subgroup, pneumonia and sepsis were the 2 most frequent causes of death, similar to what we found in the whole group. The percentage of death associated with pneumonia was even a little higher in the subgroup submitted to autopsy. In contrast, the percentage of sepsis was higher in the whole group (data not shown). We also found 101 DC considering RA as an NUCD, and in this subgroup the frequency of UCD was also similar to the whole group (data not shown).

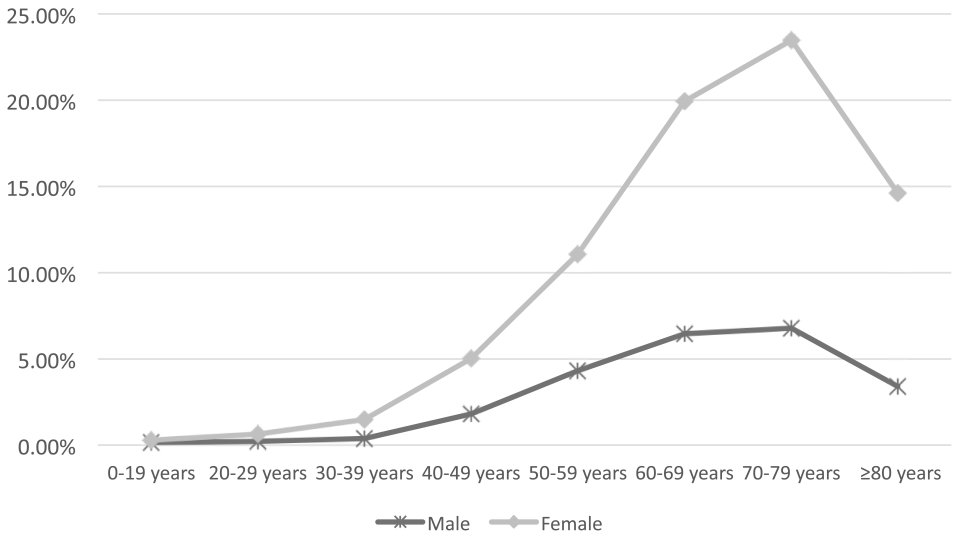

Figure 1. Percentage of rheumatoid arthritis–related deaths, according to sex and age, state of São Paolo, Brazil, 1996–2010.

Table 2. Nonunderlying causes of death when rheumatoid arthritis was the underlying cause, by period, age-adjusted, state of São Paulo, Brazil, 1996–2010. Values are given as n (%).

Nonunderlying Causes of Death	ICD-10	Total, 1996–2010	Subperiod I	Subperiod II	p
Pneumonia due to bacteria and other infectious organisms	J13.0–J16.8/J18.0–J18.9	424 (38.8)	47 (16)	279 (56.2)	< 0.001
Sepsis	A40.0–A41.9	324 (29.7)	36 (12.2)	218 (43.9)	< 0.001
Renal failure	N17–N19	125 (11.4)	27 (9.2)	67 (13.5)	0.072
Other interstitial pulmonary diseases	J84.0–J84.9	119 (10.9)	31 (10.5)	51 (10.2)	0.895
Heart failure	I50.0–I50.9	100 (9.1)	39 (13.3)	34 (6.8)	0.002
Hypertensive diseases	I10–I15	83 (7.6)	15 (5.1)	41 (8.2)	0.096
Chronic lower respiratory diseases except asthma and bronchiectasis	J40.0–J44.9	44 (4)	10 (3.4)	18 (3.6)	0.874
Urinary tract infection, site not specified	N39.0	38 (3.4)	6 (2)	19 (3.8)	0.167
Myocardial infarction	I21.0–I22.9	33 (3)	9 (3)	16 (3.2)	0.905
Complications of procedures, not elsewhere classified	T81.0–T81.9	30 (2.7)	3 (1)	17 (3.4)	0.038
Gastrointestinal hemorrhage	K92.0–K92.2	26 (2.3)	11 (3.7)	8 (1.6)	0.058
Stroke	I63.0–I64.0	25 (2.2)	14 (4.7)	4 (0.8)	< 0.001
Surgical operation with implant of artificial internal device	Y83.1	25 (2.2)	3 (1)	17 (3.4)	0.038
Tuberculosis	A15.0–A19.9	3 (0.2)	2 (0.6)	0 (0)	0.138
Total deaths		1091 (100)	293 (100)	496 (100)	

ICD10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

DISCUSSION

Considering that guidelines reinforce the necessity of tight control with early and aggressive treatment to control the inflammatory process[14,15,16,17] and prevent articular destruction, as well as to reduce extraarticular involvement in RA, we studied certain aspects concerning RA-related death, using the multiple-cause-of-death method and analyzing 2 specific subperiods.

With this method, we could increase the number of studied DC 3.6-fold, considering that a majority of RA-related deaths were described as NUCD.

In our present study, after evaluating 15 years (1996-2010) of mortality data from DC (n = 3955) issued in the state of São Paulo, we found that RA-related deaths represent 0.1% of deaths in the state. Ziadé, *et al*[18], using the same method, evaluated 32 years (1970-2002) in France and found RA mentioned in 0.22% of DC. This difference could be due to lower prevalence of RA in São Paulo state, underreporting, or both.

Circulatory system diseases were the most frequent cause of death when RA was the NUCD (1001 DC). Considering RA as the UCD, these causes were less frequent. It could be

Table 3. Underlying causes of death when RA was the nonunderlying cause, by period, age-adjusted, state of São Paulo, Brazil, 1996–2010. Values given as n (%).

Underlying Causes of Death	ICD-10	Total, 1996–2010	Subperiod, 1996–2000	Subperiod, 2006–2010	p
Certain infectious and parasitic diseases	A00-B99	162 (5.6)	46 (5.4)	56 (5.7)	0.787
Tuberculosis	A15-A19	16 (0.5)	3 (0.3)	5 (0.5)	0.732
Neoplasms	C00-D48	143 (5)	30 (3.5)	66 (6.7)	0.002*
Malignant neoplasm of bronchus or lung, unspecified	C34.9	20 (0.7)	3 (0.3)	10 (1)	0.091
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	131 (4.6)	28 (3.3)	54 (5.5)	0.023*
Immunodeficiency, unspecified	D84.9	39 (1.3)	6 (0.7)	17 (1.7)	0.049*
Diseases of the nervous system	G00-G99	45 (1.5)	7 (0.8)	24 (2.4)	0.007*
Diseases of the circulatory system	I00-I99	1001 (35.1)	328 (38.9)	336 (34.5)	0.051
Hypertensive diseases	I10-I15	121 (4.2)	38 (4.5)	45 (4.6)	0.909
Ischemic heart diseases	I20-I25	329 (11.5)	111 (13.1)	115 (11.8)	0.38
Heart failure	I50	88 (3)	30 (3.5)	26 (2.6)	0.274
Cerebrovascular diseases	I60-I69	159 (5.5)	54 (6.4)	54 (5.5)	0.438
Diseases of the respiratory system	J00-J99	621 (21.8)	207 (24.5)	146 (15)	< 0.001*
Pneumonia, organism unspecified	J18	251 (8.8)	103 (12.2)	1 (0.1)	< 0.001*
Chronic lower respiratory diseases	J40-J47	184 (6.4)	50 (5.9)	72 (7.4)	0.215
Other interstitial pulmonary diseases	J84	69 (2.4)	14 (1.6)	40 (4.1)	0.002*
Diseases of the musculoskeletal system and connective tissue	M00-M99	61 (2.1)	6 (0.7)	25 (2.5)	0.002*
Diseases of the genitourinary system	N00-N99	161 (5.6)	47 (5.5)	70 (7.1)	0.163
Renal failure	N17-N19	53 (1.8)	29 (3.4)	18 (1.8)	0.033*
Urinary tract infection, site not specified	N39.0	66 (2.3)	10 (1.1)	34 (3.4)	0.001*
External causes of morbidity and mortality	V01-Y98	34 (1.1)	6 (0.7)	22 (2.2)	0.008*
Total deaths		2847 (100)	842 (100)	973 (100)	

ICD-10 chapters are given in bold face. * $p < 0.05$. ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision; RA: rheumatoid arthritis.

that the descriptor physician would recognize the most severe disease as the main cause of death, neglecting other chronic diseases. For example, when a patient with RA dies with myocardial infarction (MI), the physician would describe MI as the UCD a majority of the time, sometimes neglecting to describe RA. The O/E ratio was equal to 1, as observed by Ziadé, *et al*[18] and reported in the literature review by Symmons and Gabriel[19]. Generally, as described by other authors[5,20,21], cardiovascular disease (CVD) remained the most important cause of death in RA in our study.

Despite its overall low frequency in the DC, stroke was less often described in the second subperiod as UCD or NUCD with RA. This could suggest that better treatment was associated with decreasing stroke in the last subperiod. However, the O/E ratio was lower than 1 for both subperiods, and that could be due to underreporting.

Similarly to the findings of Sihvonen, *et al*, the most frequent infections described in RA-related deaths were pneumonia and sepsis[20], which were in our study the main related causes of death when RA was UCD, for the entire period. The increased frequency for the last subperiod could be a result of more aggressive therapy leading to infections and deaths or a shift in the pattern of description. When RA was considered NUCD, death was due to infections (pneumonia and sepsis) in just 12% of DC data. Comparing the subperiods, pneumonia was less reported in the latter; likely because of the physician having understood that infection was a result of RA or its therapy; thus, RA was considered as a UCD. The O/E ratio for the entire studied period was > 1 for pneumonia and sepsis, suggesting that in general, infections and RA were related.

Renal failure was the third most common NUCD due to RA. Otherwise, when renal failure was the UCD, there was a significant decrease for the last subperiod. This could be due to the decrease in the use of nonsteroidal antiinflammatory drugs and the reduction in the frequency of amyloidosis [for entire period of study: 5 and 1 death(s) when RA was described as UCD and NUCD, respectively]. Despite this, the O/E was > 1. Corroborating this was the Hickson, *et al* study[22], which stated that patients with RA are more likely to develop reduced kidney function than persons without RA.

According to Bongartz, *et al*, in a population-based study, patients with RA have a higher risk of developing interstitial lung disease (ILD) than the general population and generally have a worse survival rate compared with RA patients without ILD[23]. Among risk factors to develop RA-related ILD, male sex is one of the greatest[23,24]. In our study, we found that ILD was an important cause of death, which had a significant increase of description as UCD (RA as NUCD) in the second subperiod. In addition, the O/E ratio was > 1,

Table 4. Observed/expected ratios for underlying causes of death in rheumatoid arthritis (RA), adjusted for age, by time periods, state of São Paulo, Brazil.

Underlying Cause of Death	Total, 1996–2010	Subperiod 1996–2000	Subperiod 2006–2010
Tuberculosis	1.08 (0.66–1.76) [16]	0.5 (0.16–1.55) [03]	1.37 (0.56–3.29) [05]
Sepsis	3.45 (2.74–4.33) [74]	4.04 (2.73–5.98) [25]	2.98 (1.95–4.58) [22]
Mycoses*	8.29 (4.44–15.43) [10]	8.05 (2.58–25.06) [03]	11.14 (4.16–29.82) [10]
Neoplasms	0.3 (0.25–0.34) [143]	0.23 (0.15–0.32) [30]	0.37 (0.29–0.47) [66]
Malignant neoplasm of stomach	0.2 (0.1–0.39) [9]	0.15 (0.03–0.58) [02]	0.21 (0.06–0.66) [03]
Malignant neoplasm of bronchus and lung	0.32 (0.2–0.5) [19]	0.19 (0.06–0.59) [03]	0.46 (0.24–0.85) [10]
Lymphoma	0.7 (0.36–1.35) [9]	0.84 (0.26–2.59) [03]	0.89 (0.33–2.36) [04]
Diabetes	1.04 (0.86–1.25) [111]	1.05 (0.74–1.49) [32]	1.05 (0.77–1.43) [40]
Cushing syndrome	133.37 (52.88–336.3) [5]	96.04 (12.56–734.15) [01]	67.79 (9.05–507.85) [01]
Diseases of the circulatory system	1.07 (1.0–1.13) [1001]	1.14 (1.02–1.27) [328]	1.08 (0.96–1.16) [336]
Acute myocardial infarction, unspecified	0.94 (0.82–1.07) [218]	0.97 (0.76–1.22) [69]	1.01 (0.81–1.26) [78]
Heart failure	1.07 (1.07–1.32) [88]	1.01 (0.70–1.43) [30]	1.05 (0.71–1.54) [26]
Stroke**	0.61 (0.48–0.75) [76]	0.67 (0.47–0.94) [33]	0.47 (0.29–0.74) [18]
Pneumonia	1.74 (1.54–1.96) [269]	2.86 (2.36–3.44) [109]	0.13 (0.06–0.25) [08]
Chronic obstructive respiratory diseases***	1.56 (1.34–1.81) [169]	1.43 (1.06–1.90) [46]	1.86 (1.45–2.36) [66]
Other interstitial pulmonary diseases	11.34 (8.95–14.38) [69]	8.24 (4.55–14.91) [11]	14.47 (10.54–19.83) [39]
Digestive ulcer****	3.11 (2.23–4.33) [35]	2.96 (1.64–5.35) [11]	2.61 (1.35–5.02) [9]
Pyogenic arthritis	49.55 (31.31–78.42) [19]	22.50 (5.55–91.07) [02]	61.02 (29.99–124.01) [08]
Renal failure	1.87 (1.42–2.45) [53]	3.39 (2.35–4.87) [29]	1.91 (1.2–3.02) [18]

Numbers in parentheses are 95% CI. Numbers in brackets refer to observed number of the specific underlying causes of death and mention of RA. * Mycoses, except dermatophytosis (B35) and other superficial mycoses (B36). **Cerebral infarction (I63) and Stroke, not specified as hemorrhage or infarction (I64). *** Block chronic lower respiratory diseases (J40-J47), except Asthma (J45), Status asthmaticus (J46) and Bronchiectasis (J47). ****Digestive ulcer (K25-K28): Gastric ulcer (K25), Duodenal ulcer (K26), Peptic ulcer — site unspecified (K27), and Gastrojejunal ulcer (K28).

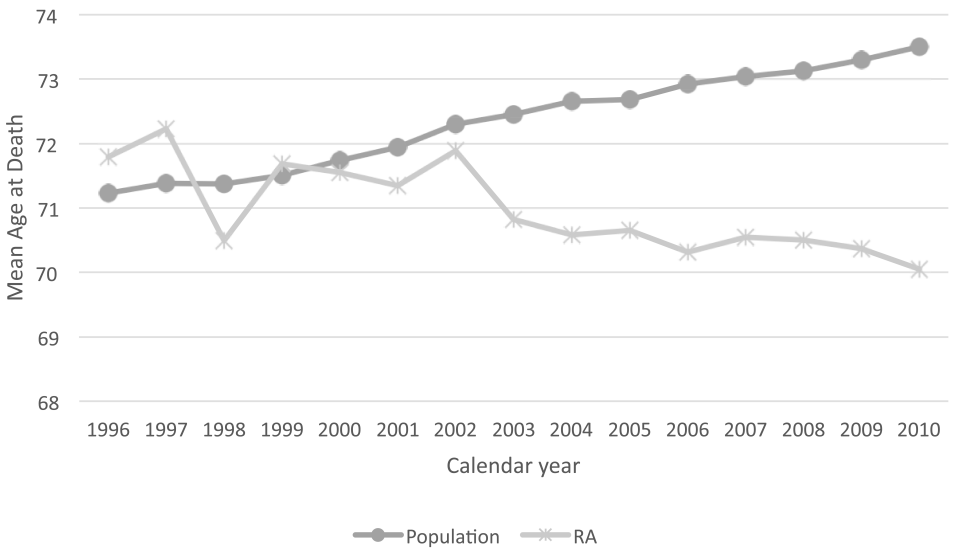

Figure 2. Trend of mean age at death on death certificates with any mention of rheumatoid arthritis (RA) and in the general population, for death at age at least 50 years, state of São Paolo, Brazil, 1996–2010.

with the highest levels for men (for entire period, O/E 16.98; 95% CI 11.16-25.82).

For neoplasm, as expected, when RA was a UCD, we observed a lower frequency of descriptions. This was likely due to neoplasm being considered as the main cause of death, and similar to what we observed for CVD, RA was forgotten. When RA was the NUCD, described neoplasms remained few; however, there was an increased level for the last subperiod. This was similar to the study by Ziadé, *et al*[18], with O/E < 1 for neoplasms. In our study, lymphoma and prostatic cancer had O/E ratio = 1. Considering that lymphoproliferative disorder risk was associated with RA[25], we would expect higher frequencies, which were not observed. This again brings up the possibility of underreporting in RA-related deaths.

Despite the expectation of higher frequency of tubercu-

losis, mainly in the last subperiod, we found O/E > 1, just for females in the entire period. Considering that most studies show association between tuberculosis and RA[26], we can speculate the underreporting of tuberculosis in RA-related deaths.

The O/E ratio for chronic obstructive pulmonary disease was > 1 for both subperiods, corroborating the Nannini, *et al* study[27].

With more aggressive therapy and better disease control, we should see an increase in life expectancy. But we observed a decrease in the mean age at RA-related deaths, mainly since 2003. This was an opposite trend compared to the general population of São Paulo state. This result was completely different from what was observed in France[18], where the mean age at death rose. One possible explanation can be the socioeconomic difference between populations, including healthcare access. The observation of increased infections in the second subperiod suggests that more aggressive treatment of RA in the more recent years could be associated with risk of earlier death in a population with higher risk of infections and the difficulty of accessing early treatment of this complication.

Mortality statistics present 2 limitations regarding the DC: quantitative and qualitative. Regarding DC number, in São Paulo state there is almost 100% coverage, with adequate reporting of deaths[28,29]. Concerning DC quality in São Paulo state during the period 1996 to 2007, only 6.4% of cases had ill-defined causes[7]. Another variable of DC quality is the number of causes mentioned per DC; in our study it was 4.2 for the entire period for any mention of RA.

The strength of our study was the coverage of DC throughout the state of São Paulo, allowing the inclusion of all deaths that occurred in different local healthcare areas, reducing selection bias. Further, the long period of study permitted comparisons between subperiods, when different therapeutic guidelines were followed.

The cause of deaths found in the subgroup submitted to autopsy were similar to those described in the whole group, reinforcing the reliability of our study.

Because we used DC-sourced data for this study, some limitations were intrinsically related to the method, such as underreporting and inadequate DC description.

An unexpected early occurrence of RA-related deaths in the state of São Paulo was found. CVD remained an important cause of death in RA, justifying a judicious followup and treatment of CV risk factors. Infectious diseases are an important cause of death in patients with RA, raising the question of whether infections are related to more vigorous immunosuppressive treatment, as recommended by recent guidelines.

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REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
2. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:269-81.
3. Senna ER, De Barros AL, Silva EO, Costa IF, Pereira LV, Ciconelli RM, et al. Prevalence of rheumatic diseases in Brazil: a study using the COPCORD approach. J Rheumatol 2004;31:594-7.
4. Marques-Neto JF, Gonçalves ET, Langen LFdOB, Cunha MdFL, Radominski S, Oliveira SMd, et al. [Multicenter study of the prevalence of rheumatoid arthritis in adult samples of the Brazilian population]. [Article in Portuguese] Rev Bras Reumatol 1993;33:169-73.
5. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008;26 Suppl 51:S35-61.
6. Souza DC, Santo AH, Sato EI. Mortality profile related to systemic lupus erythematosus: a multiple cause-of-death analysis. J Rheumatol 2012;39:496-503.
7. Santo AH, Souza JM, Pinheiro CE, Souza DC, Sato EI. Trends in dermatomyositis- and polymyositis-related mortality in the state of Sao Paulo, Brazil, 1985-2007: multiple cause-of-death analysis. BMC Public Health 2010;10:597.
8. Israel RA, Rosenberg HM, Curtin LR. Analytical potential for multiple cause-of-death data. Am J Epidemiol 1986;124:161-79.
9. Coste J, Jougla E. Mortality from rheumatoid arthritis in France, 1970-1990. Int J Epidemiol 1994;23:545-52.
10. [Brazilian Institute of Geography and Statistics - Synthesis of São Paulo State]. [In Portuguese. Internet. Accessed August 26, 2015.] Available from: www.ibge.gov.br/estadosat/perfil.php?sigla=sp
11. [Table 01 - Gross Domestic Product - GDP and participation of Major Regions and Federative Units]. [In Portuguese. Internet. Accessed August 26, 2015.] Available from: www.ibge.gov.br/home/estatistica/economia/contasregionais/2010/default_pdf.shtm
12. World Health Organization. International statistical classification of diseases and related problems, 10th revision, volume 1. Geneva: World Health Organization; 2010.
13. [Ministry of Health. Health information - Demographic and Socioeconomic. Resident population - São Paulo]. [In Portuguese. Internet. Accessed August 26, 2015.] Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?ibge/cnv/popsp.def
14. Albers JM, Paimela L, Kurki P, Eberhardt KB, Emery P, van't Hof MA, et al. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:453-8.
15. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
16. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
17. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
18. Ziadé N, Jougla E, Coste J. Population-level influence of rheumatoid arthritis on mortality and recent trends: a multiple cause-of-death analysis in France, 1970-2002. J Rheumatol 2008;35:1950-7.
19. Symmons DP, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011;7:399-408.

20. Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. Scand J Rheumatol 2004;33:221-7.
21. Myasoedova E, Davis JM 3rd, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. Curr Rheumatol Rep 2010;12:379-85.
22. Hickson LJ, Crowson CS, Gabriel SE, McCarthy JT, Matteson EL. Development of reduced kidney function in rheumatoid arthritis. Am J Kidney Dis 2014;63:206-13.
23. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583-91.
24. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology 2014;53:1676-82.
25. Turesson C, Matteson EL. Malignancy as a comorbidity in rheumatic diseases. Rheumatology 2013;52:5-14.
26. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009;11:229.
27. Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, Vassallo R, et al. Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study. Arthritis Care Res 2013;65:1243-50.
28. [Ministry of Health. Interagency Network of Information for Health Indicators and Basic Data - Brazil. Coverage indicators. Ratio between reported and estimated deaths. Years 1991-2000]. [In Portuguese. Internet. Accessed August 26, 2015.] Available from: http://tabnet.datasus.gov.br/cgi/idb2011/a1801a.htm
29. [Ministry of Health. Interagency Network of Information for Health Indicators and Basic Data - Brazil. Coverage indicators. Ratio between reported and estimated deaths. Years 2000-2010]. [In Portuguese. Internet. Accessed August 26, 2015.] Available from: http://tabnet.datasus.gov.br/cgi/idb2011/a1801b.htm