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BRIEF REPORT

Distinct mortality profile in systemic sclerosis: a death certificate study in Rio de Janeiro, Brazil (2006–2015) using a multiple causes of death analysis

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Abstract
The objective of this study was to assess the mortality profile related to SSc in the state of Rio de Janeiro, Brazil. We retrospectively examined all registered deaths in the region (2006–2015 period) in which the diagnosis of SSc was mentioned on any line of the death certificates (underlying cause of death [UCD], $n = 223$; non-UCD, $n = 151$). Besides the analysis of gender, age, and the causes of death, we also compared the mortality from UCDs between individuals whose death causes included SSc (cases) and those whose death causes did not include SSc (deceased controls). For the latter comparison, we used the mortality odds ratio to approximate the cause-specific standardized mortality ratio. We identified 1495 death causes among the 374 SSc cases. The mean age at death of the SSc cases (85% women) was significantly lower than that of the controls ($n = 1{,}294{,}117$) (58.7 vs. 65.5 years, respectively). The main death causes were circulatory system diseases, infections, and respiratory diseases (36%, 34%, and 21% of SSc cases, respectively). Compared to the deceased controls, there were proportionally more deaths among the SSc cases from pulmonary arterial hypertension, lung fibrosis, septicemia, gastrointestinal hemorrhage, other systemic connective tissue diseases, and heart failure (for death age < 50 years). We confirmed the high burden of cardiovascular, respiratory, and infectious causes in this predominantly non-Caucasian sample of SSc patients. Of interest, the percentage of infection-related deaths in our report was about three times higher than that in SSc studies with predominantly Caucasian populations.

Keywords Causes of death · Infections · Mortality · Mortality profile · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease that is associated with a high risk of mortality [1]. To date, most studies on mortality in this chronic disease have been performed in predominantly Caucasian populations [2–10], with scarce data available from other ethnic groups. Of note, prior works have mostly investigated the primary cause of death (also referred to as underlying cause of death [UCD]) and its relation with SSc itself, paying less attention to the impact on mortality of other possible contributing conditions. In performing a multiple causes of death analysis, seldom used in assessments of mortality in diffuse connective tissue disorders [10–12], all conditions directly and indirectly involved in the death process are taken into account, i.e., not just the UCD, thus deepening our knowledge on SSc deaths.

Therefore, we performed a retrospective death certificate (DC)-based study on the mortality profile in SSc in the state of Rio de Janeiro, Brazil, by using a multiple causes of death approach.

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Materials and methods

Data collection

To conduct this study, we were granted access to limited data by the state of Rio de Janeiro Vital Statistics Bureau on all registered deaths in the region from 2006 to 2015. In addition to collecting all DCs issued in that area, the Bureau assigns a code to each cause of death and also selects the UCD among all diseases and conditions entered by the physician on the DC. All processes of coding and classification of causes of death are performed according to the guidelines of the tenth revision of the International Classification of Diseases (ICD-10). This study was approved by our institutional ethics committee (number 077118/2017).

Definitions

According to the World Health Organization [13], UCD is defined as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Immediate and intermediate causes of death respectively mean "the final disease or condition resulting in death" and "the disease(s), condition(s), or complication(s) that occur(s) somewhere in time between the underlying and the immediate cause of death." These events are reported in part I of the cause-of-death section of the DC, whereas part II reports the contributory causes of death, i.e., "all other significant diseases, conditions, or injuries that contributed to death but did not result in the UCD." The immediate cause of death and all other intermediate and contributory conditions are collectively called the "non-underlying causes of death" (non-UCDs), whereas "multiple causes of death" refers to the sum of the death causes in both parts of the DC.

Identification of SSc deaths

In order to collect data on such deaths (2006–2015 period) from the database provided by the state of Rio de Janeiro Vital Statistics Bureau, we looked for the following ICD-10 codes for SSc: M34.0, M34.1, M34.2, M34.8, and M34.9.

Objectives

We primarily aimed to analyze all causes of death reported in the setting of SSc as UCD, as well as when listed as a non-UCD. In addition, we compared the mortality from UCDs (all-age deaths, age at death < 50 years, and age at death ≥ 50 years) between individuals who had SSc listed as one of their causes of death (SSc cases) and those who had no mention of SSc as one of their causes of mortality (deceased controls). Secondarily, we evaluated for differences in demographic characteristics between the cases and controls, and also among the SSc cases for each cause of mortality.

Statistical analysis

Causes of death were examined using standard descriptive statistics. Categorical variables are shown as a number (percentage), and differences were compared with a chi-square test, whereas continuous variables are presented as a mean (standard deviation), and differences were evaluated by Student's t test. The mortality odds ratio, as proposed by Miettinen and Wang [14], was used to approximate the cause-specific standardized mortality ratio, then calculated as follows: [(number of cause-specific deaths among the SSc cases x number of deaths for other causes among the deceased controls)/(number of deaths for other causes among the SSc cases x number of cause-specific deaths among the deceased controls)]. This statistics is useful when death data are available but the population at risk is not known. P values < 0.05 were considered statistically significant. Statistical analyses were performed with STATISTICA software version 8.0 (StatSoft, Tulsa, OK).

Results

Over the course of a 10-year period (2006–2015), SSc was reported in 374 (0.02%) out of 1,294,491 DCs issued in the state of Rio de Janeiro, and was the UCD for 223 patients and the non-UCD for 151. On average, each DC contained 3.9 diagnoses (range 1–11), totaling 1495 death causes (including 374 mentions of SSc). The mean [standard deviation] age at death (range 18–92 years) of the SSc cases ($n = 374$) was significantly lower (58.7 [15.6] years vs. 65.5 [19.63] years, respectively; $p < 0.0001$) than that of the controls ($n =$ 1,294,117). The age at the time of death was available for 1,252,102 subjects, mostly at ≥ 50 years ($n = 987{,}552$). With regard to gender, men (15%, $n = 56/374$) died prematurely compared to women (85%, $n = 318/374$) (53.5 [13.8] years vs 59.6 [15.7] years, respectively; $p = 0.004$).

SSc as UCD ($n = 223$ deaths)

In this setting, we evaluated the immediate, intermediate, and contributory causes of death (i.e., the non-UCDs) of each SSc case. Infections (namely septicemia and pneumonia) were the leading cause of death, followed by pulmonary fibrosis, hypertensive diseases, renal failure, and pulmonary arterial hypertension (PAH) (Table 1). Malignancy (breast origin) and tuberculosis were each mentioned once as non-UCD (data not shown). There was no difference between the sexes concerning the percentage of total deaths from each of the non-UCDs. On the other hand, the average age at death due

Table 1 Non-underlying causes of death among individuals who had systemic sclerosis reported as their underlying (or primary) cause. Data from the state of Rio de Janeiro Vital Statistics Bureau (2006–2015 period)

Non-underlying cause of death	ICD-10 code	Total deaths ($n = 223$)		Women's deaths ($n = 187$)		Men's deaths ($n = 36$)		p1/p2[a]
		Number of patients (%)	Mean (SD) age at death (years)	Number of patients (%)	Mean (SD) age at death (years)	Number of patients (%)	Mean (SD) age at death (years)	
Septicemia[b]	A40, A41	84 (37.6)	56.6 (17.0)	72 (38.5)	58.4 (16.7)	12 (33.3)	46 (15.6)	0.55/0.02
Pneumonia due to bacteria and other infectious organisms	J13-J16, J18	72 (32.2)	55.9 (16.4)	58 (31)	57.3 (16.7)	14 (38.8)	50.2 (14.2)	0.35/0.12
Pulmonary fibrosis[c]	J84.1	39 (17.4)	58.5 (12.6)	33 (17.6)	59.5 (13)	6 (16.6)	53 (8.9)	0.88/0.16
Hypertensive diseases	I10-I15	26 (11.6)	61.9 (16.4)	22 (11.7)	62.1 (17.2)	4 (11.1)	61 (12.3)	0.91/0.85
Renal failure	N17-N19	21 (9.4)	53.2 (16.8)	17 (9.0)	52.5 (17.9)	4 (11.1)	56.5 (12.1)	0.69/0.61
Pulmonary arterial hypertension	I27.0, I27.2	17 (7.6)	55.2 (15.3)	12 (6.4)	55.3 (18.2)	5 (13.8)	55 (5.6)	0.12/0.95

We only report diseases that accounted for ≥ 5% of total deaths. The following ICD-10 categories were excluded from this analysis: "Symptoms, signs, and abnormal clinical and laboratory findings," "Injury, poisoning, and certain other consequences of external causes," "External causes of morbidity," and "Factors influencing health status and contact with health services"

ICD-10 Tenth Revision of the International Classification of Diseases, *SD* standard deviation

[a] *P* values refer to the between-sex difference for the proportion of deaths (p1) and mean age at death (p2) for each non-underlying cause of death (by chi-square and Student's *t* test, respectively)

[b] Forty-five of these patients also had pneumonia listed as one of their causes of death

[c] Four of these patients also had pulmonary arterial hypertension listed as one of their causes of death

to septicemia was significantly lower in men in comparison with women (Table 1).

SSc as non-UCD ($n = 151$ deaths)

In this scenario, we examined the primary cause of death of each SSc case. As illustrated in Table 2, the main UCDs were PAH, malignancies (most commonly from bronchi and lungs), and septicemia. Pneumonia was cited only once as UCD (data not shown). The proportion of deaths from each UCD was similar between the sexes. Except for hypertensive diseases, there were no meaningful differences between the sexes concerning the average age at death from the other UCDs.

All SSc deaths ($n = 374$)

Table 3 shows the mortality odds ratios (relative to UCDs) between the SSc cases ($n = 374$) and the deceased controls ($n = 1{,}294{,}117$). Concerning all-age deaths and also those occurred at ≥ 50 years, there were proportionally more deaths among the SSc cases from the following conditions: PAH, septicemia, gastrointestinal hemorrhage, other systemic connective tissue diseases (CTDs), and pulmonary fibrosis. Deaths due to heart failure were proportionally more frequent in the group of cases only at age < 50 years. On the other hand, the following conditions were significantly less reported as UCDs among the SSc cases (all-age deaths): diseases of the circulatory system in general, hypertensive diseases, acute myocardial infarction, malignant neoplasms, endocrine/nutritional/metabolic diseases, and disorders of the genitourinary system. Of these, only cancer mortality was proportionally less often in this group at age below 50 years.

Discussion

In this study, we examined more than 1000 causes of death that were in some way related to SSc, figures that are much greater than if we had simply investigated the single primary cause of death of each SSc case, as has traditionally been done. When employing this type of analysis, all diseases and conditions directly and indirectly contributing to death are considered, thus broadening our understanding of the disease's natural course.

Our major findings were as follows: (1) a clear predominance of SSc deaths from circulatory system diseases and infections (namely pneumonia and septicemia) over pulmonary diseases (namely PAH and lung fibrosis) and malignancies, as determined by the sum of each as UCD as well as non-UCD (36%, 34%, 21%, and 4.5% of SSc cases, respectively) and (2) an excess mortality in SSc from PAH, septicemia, gastrointestinal hemorrhage, pulmonary fibrosis, other systemic CTDs, and heart failure (for death age < 50 years), as

Table 2 Underlying (or primary) cause of death among individuals who had systemic sclerosis reported as a non-underlying cause. Data from the state of Rio de Janeiro Vital Statistics Bureau (2006–2015 period)

Underlying cause of death	ICD-10 code	Total deaths ($n = 151$)		Women's deaths ($n = 131$)		Men's deaths ($n = 20$)		p1/p2[a]
		Number of patients (%)	Mean (SD) age at death (years)	Number of patients (%)	Mean (SD) age at death (years)	Number of patients (%)	Mean (SD) age at death (years)	
Pulmonary arterial hypertension	I27.0, I27.2	20 (13.2)	58.1 (13.3)	18 (13.7)	57.6 (13.7)	2 (10)	63 (9.8)	0.65/0.57
Neoplasms[b]	C00-D48	16 (10.5)	63.6 (7.8)	12 (9.1)	64.2 (8.9)	4 (20)	61.7 (3.5)	0.14/0.44
Septicemia	A40-A41.9	15 (9.9)	62.2 (18)	14 (10.6)	62 (18.7)	1 (5)	65	0.43/–
Other systemic connective tissue diseases	M30-M33, M35, M36	10 (6.6)	46.1 (13.3)	9 (6.8)	46.5 (14)	1 (5)	42	0.76/–
Pulmonary fibrosis	J84.1	7 (4.6)	69.4 (11.2)	7 (5.3)	69.4 (11.2)	0	–	0.29/–
Hypertensive diseases	I10-I15	6 (3.9)	66 (14.2)	4 (3.0)	74 (11.1)	2 (10)	52 (5.6)	0.13/0.03
Heart failure[c]	I50	6 (3.9)	52.1 (11.3)	5 (3.8)	52.8 (12.5)	1 (5)	49	0.79/–
Gastrointestinal hemorrhage	K92.0-K92.2	6 (3.9)	72.5 (3.6)	5 (3.8)	72.8 (4)	1 (5)	71	0.79/–

The following ICD-10 categories were excluded from this analysis: "Symptoms, signs, and abnormal clinical and laboratory findings," "Injury, poisoning, and certain other consequences of external causes," "External causes of morbidity," and "Factors influencing health status and contact with health services"

ICD-10 Tenth Revision of the International Classification of Diseases, *SD* standard deviation

[a] *P* values refer to the between-sex difference for the proportion of deaths (p1) and mean age at death (p2) for each underlying cause of death (by chi-square and Student's *t* test, respectively)

[b] All 16 cases were malignant neoplasms; 6 of the bronchi and lungs, 3 of the ovaries, 2 of the breast, and 1 case each of the esophagus, colon, mediastinum, uterus, and pleura

[c] None of the cases were associated with pulmonary arterial hypertension and/or pulmonary fibrosis

Table 3 Mortality odds ratios (95% confidence interval) between the SSc cases ($n = 374$) and the deceased controls ($n = 1{,}294{,}117$). Only clinically significant data related to underlying (or primary) causes of death are presented. Mortality data from the state of Rio de Janeiro Vital Statistics Bureau (2006–2015 period)

Increased proportional mortality among the SSc cases (vs deceased controls)				
Underlying cause of death	ICD-10 code	All-age deaths	Age at death < 50 years	Age at death ≥ 50 years
Pulmonary arterial hypertension	I27.0, I27.2	138.94 (87.84–219.77) $P < 0.0001$	76.60 (30.81–190.45) $P < 0.0001$	165.22 (97.14–281.01) $P < 0.0001$
Other systemic connective tissue diseases	M30-M33, M35, M36	21.57 (11.48–40.50) $P < 0.0001$	24.24 (11.21–52.38) $P < 0.0001$	12.96 (4.14–40.51) $P < 0.0001$
Pulmonary fibrosis	J84.1	11.05 (5.22–23.37) $P < 0.0001$	13.51 (0.83–219.11) $P = 0.06$	12.28 (5.79–26.04) $P < 0.0001$
Heart failure	I50	0.82 (0.36–1.84) $P = 0.63$	6.40 (2.35–17.43) $P = 0.0003$	0.30 (0.07–1.23) $P = 0.09$
Gastrointestinal hemorrhage	K92.0-K92.2	2.40 (1.07–5.37) $P = 0.03$	1.59 (0.09–25.69) $P = 0.74$	2.81 (1.25–6.32) $P = 0.01$
Septicemia	A40-A41.9	1.92 (1.14–3.21) $P = 0.01$	1.61 (0.39–6.56) $P = 0.50$	2.0 (1.14–3.49) $P = 0.01$
Decreased proportional mortality among the SSc cases (vs deceased controls)				
Underlying cause of death	ICD-10 code	All-age deaths	Age at death < 50 years	Age at death ≥ 50 years
Diseases of the circulatory system	I00-I99	0.46 (0.35–0.61) $P < 0.0001$	1.04 (0.59–1.84) $P = 0.86$	0.38 (0.28–0.53) $P < 0.0001$
Hypertensive diseases	I10-I15	0.35 (0.15–0.78) $P = 0.01$	0.61 (0.08–4.43) $P = 0.63$	0.32 (0.13–0.79) $P = 0.01$
Acute myocardial infarction	I21	0.16 (0.06–0.40) $P = 0.0001$	0.25 (0.03–1.83) $P = 0.17$	0.15 (0.05–0.41) $P = 0.0002$
Malignant neoplasms	C00-C97	0.25 (0.15–0.41) $P < 0.0001$	0.04 (0.002–0.70) $P = 0.02$	0.30 (0.18–0.50) $P < 0.0001$
Endocrine, nutritional, and metabolic diseases	E00-E90	0.15 (0.05–0.42) $P = 0.0002$	0.67 (0.16–2.72) $P = 0.57$	0.09 (0.02–0.36) $P = 0.0007$
Diseases of the genitourinary system	N00-N99	0.34 (0.13–0.93) $P = 0.03$	0.38 (0.02–6.12) $P = 0.49$	0.40 (0.15–1.08) $P = 0.07$

well as a shortened lifespan (especially in men), compared to the deceased controls from the general population.

According to previous studies on the mortality profile in SSc [2–10, 15], the cardiopulmonary system was shown to be the leading cause of mortality. In 2010, Tyndall et al. reported on the deaths of 234 out of 5860 prospectively followed patients (up to April 2008) from the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) registry [7]. Of these deaths, 59% were due to pulmonary (PAH + lung fibrosis) and cardiocirculatory system diseases, followed by malignancies and infections (13% each). In the most recent analysis of the EUSTAR database (up to May 2014), then totalling 1072 deaths, cardiac disease (27%) and respiratory causes (17%) were attributed as the main offenders in SSc, similarly to the results observed in France in a multiple causes of death analysis of 2719 DCs related to SSc (31% and 18%, respectively) [10]. Noteworthy, infections ranked, respectively, as the third and fourth most common cause of death in the DCs and in the EUSTAR samples (11% and 9%, respectively) [10], with the infection-related percentage of overall deaths in both samples being approximately one third of that (34%) encountered in our multiple causes of death study. However, Elhai et al. [10] showed a significantly higher rate of infectious fatalities (notably from the lungs) among the SSc patients compared with the general population, which we also demonstrated in our report for sepsis-related deaths (Table 3).

Of interest, a Brazilian study performed in the state of São Paulo reported results opposite to ours, wherein lung involvement and diseases of the cardiocirculatory system accounted for most of the 168 deaths of SSc patients (31.5% and 20.8%, respectively), with infections (namely septicemia) being responsible for 14% of the fatalities [15]. With respect to such discrepancy, we believe that the better overall functioning of the health system in the state of São Paulo, which is the richest one in Brazil, along with methodologic differences, could partly explain their lower prevalence of infectious causes of death.

In contrast to prior publications [2–5, 7, 9, 10], we and Sampaio-Barros et al. [15] have not found malignant neoplasms to be a major determinant of death among non-Caucasians, with cancer cases accounting for less than 5% of overall fatalities in both studies. Indeed, in our study, the proportion of cancer deaths was significantly lower among the SSc cases compared to the deceased controls, which could in part be justified by the earlier death age in the former group. In addition, we also observed a considerably higher mortality from other systemic CTDs in comparison with the deceased controls (9 out of 10 due to SLE), which might suggest a poorer prognosis of SSc when overlapping with SLE.

Given the rarity of SSc, we consider that the major strengths of our study were the large number of death causes analyzed in a predominantly non-Caucasian ethnic group and the methodological approach used. Indeed, more than 1000 non-underlying causes directly or indirectly related to the death process would have been overlooked if we had just examined the primary cause of mortality. However, our results may be biased by problems with accuracy and reliability of the data on the DCs [16]. Our study was also limited because we could not ascertain the SSc diagnosis, which is a limitation inherent to database studies.

To conclude, the accumulated evidence gathered from DCs analyses and adjudicated expert judgment has shown that patients with SSc face an increased risk of death from cardiovascular (especially primary heart disease), respiratory (especially PAH and interstitial lung disease), and infectious causes, thus prompting early screening of such cardiorespiratory conditions in all SSc patients, as well as immunization against certain vaccine-preventable diseases (most notably influenza and pneumococcus). Of interest, the percentage of infection-related deaths in our sample was about three times higher than that in SSc studies with predominantly Caucasian populations.

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Compliance with ethical standards This study was approved by our institutional ethics committee (number 077118/2017).

Disclosures None.

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