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ORIGINAL RESEARCH

# Comorbidity burden on mortality in patients with systemic sclerosis

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## ABSTRACT

**Introduction** Systemic sclerosis (SSc) is a serious life-threatening tissue disease. A significant aspect of its mortality arises from comorbid conditions. Our study aimed at mapping out the prevalence of these comorbidities and their relation to mortality, thus creating a 'comorbidome'.

**Methods** In our retrospective, single-centre observational study, we recorded each patient's data, including demographic informations, vital stats and SSc-related organ involvement, along with the presence or absence of 14 predefined comorbidities. We also documented the dates of their initial and most recent visits. To construct survival curves, we used the Kaplan-Meier method, followed by a Cox regression model for multivariate analysis.

**Results** Our study involved 400 participants, 74 of whom unfortunately passed away. It is important to note that three specific comorbidities showed significant correlation to mortality: neoplasia, cardiovascular diseases and polypharmacy, as well as two SSc-specific organ involvements (lung and cardiac).

**Conclusion** Our research led to the successful creation of the SSc comorbidome. Comorbidities are a major concern for patients suffering from SSc, particularly cardiovascular diseases and neoplasms. Our study highlights the effects of polypharmacy. The resultant comorbidome offers a comprehensive and analytical perspective on this complex issue and underscores the inter-relatedness of the data. Our study, however, was limited by a small sample size. Therefore, to confirm our findings, validation on a larger scale is necessary. This could potentially contribute to the creation of a future mortality scoring tool.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systemic sclerosis (SSc) can be lethal, with comorbidities worsening mortality in fragile, intensively treated patients.

### WHAT THIS STUDY ADDS

⇒ This study evaluated the comorbidity profiles of patients with SSc, alongside demographic and disease-specific characteristics.

⇒ Significant associations between neoplasia, cardiovascular diseases, polypharmacy, diabetes and mortality were validated using machine-learning methods.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underscores the need for systematic comorbidity assessment in patients with SSc, potentially guiding mortality risk scores and patient stratification.

## INTRODUCTION

Systemic sclerosis (SSc) is a rare, complex, autoimmune disease marked by an overproduction of the extracellular matrix in the skin and internal organs, leading to dysfunction.[1] It appears to arise from two combined phenomena: immune system dysregulation, signified by immunological deposits in tissues and circulating auto-antibodies, and microvascular injuries, coupled with endothelial dysfunction. These injuries manifest as either scarcity or abnormal proliferation of capillaries, depending on the tissue involved.[2]

Considered the most severe autoimmune disease, it carries a high mortality rate, up to three times higher than the general population, according to some studies.[3] A significant portion of this mortality can be attributed to serious organ complications such as interstitial lung disease (ILD), pulmonary hypertension, myocardial disease and acute kidney injury.[4] Because of its severity, much of the past research has been focused on the disease's treatment and management. Progress has been made with the introduction of immunosuppressive drugs, antifibrotic medications, vasodilators and autologous stem cell transplants, which have all contributed to reducing patients' mortality rates.

Recent studies within the European Scleroderma Trial and Research Group (EUSTAR) cohort revealed that most deaths were directly associated with SSc. However, a significant proportion of the mortality rate was also comorbidity related.[4 5] The subject of comorbidities is thoroughly researched

in other connective tissue diseases (CTD) like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), particularly in terms of cardiovascular diseases[6] and infectious complications.[7]

In 2012, Divo *et al* introduced the comorbidome of chronic obstructive pulmonary disease (COPD), a unique method used to portray the frequency and mortality rate of comorbidities in patients with COPD. This approach helped them develop a mortality score known as the COTE index (COPD specific Comorbidity TEst), which is uniquely associated with a patient's comorbidity profile.[8]

In the field of SSc, there is a knowledge gap. It is recognised that neoplasms, infections and cardiovascular diseases are frequent and influence survival rates, but precise identification of which diseases to prioritise remains elusive.[9] Furthermore, intense immunosuppressive therapies are often considered for these patients, sometimes in combination. Therefore, a thorough evaluation of the appropriateness of these treatments should account for the significance of their comorbidities.

Our primary goal was to use the comorbidome concept in SSc by determining the prevalence of each comorbidity and assessing its correlation with mortality risk in the disease.

## MATERIALS AND METHOD

### Study design and population

We conducted a retrospective, single-centre cohort study at the University Hospital of Bordeaux, France. We followed all patients screened for SSc in the departments of rheumatology, internal medicine, vascular medicine, pulmonology or dermatology between March 2012 and December 2022.

We excluded patients who did not meet the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) diagnosis criteria for SSc[10] or in case of missing critical data (patients with no precise recollection of their medical history).

### Ethics

The sponsor and investigator(s) commit to conducting this research in compliance with Law No 2004-806 of 9 August 2004, and in accordance with Good Clinical Practices (ICH, version 4; 1 May 1996, and the decision of 24 November 2006) and the Declaration of Helsinki. The data recorded during this research will be processed electronically at UMR CNRS-5164 CIRID in compliance with Law No 78-17 of 6 January 1978, on data processing, files and civil liberties, as amended by Law No 2004-801 of 6 August 2004.

### Measurements

We documented each patient's age, sex and comorbidities, excluding resolved diseases such as past infections.[11 12] SSc-related specific organ involvements were collected regarding skin and joints,[11] heart,[12] lung,[13] guts[14] and kidneys (see criteria in the online supplemental data).

### Comorbidities

Comorbidities were systematically recorded from patients' digital medical record using DxCare software. The Charlson Comorbidity Index[15] was used as reference to record relevant comorbidities. From this index, we excluded two comorbidities. First, hemiplegia, because it is a heterogenous symptom that can imply other diseases, some which were also recorded (eg, stroke, but also peripheral neuropathy…). Second, CTDs were excluded (some patients can have overlap syndrome with phenotypes of two or more CTDs, but we considered it to be one and the same disease, so it does not fit the definition of comorbidity).

We also collected the comorbidities that were, in previous studies, significantly associated with SSc or other CTDs (osteoporosis, depression and anxiety).[16] We also added some comorbidities that are nowadays considered public health problems (tobacco use, obesity). Finally, we added the notion of polypharmacy, defined in two different ways: (1) as a discrete variable (more or less than four medications[17]) for plotting survival curves, and (2) as a continuous variable for regression calculations. The details of the method of data collection for each comorbidity are explained in the online supplemental materials.

### Survival

The start of each subject's follow-up period was marked by their initial visit to one of our previously mentioned hospital departments and ended either at their last visit, their time of death or the data collection cut-off on 31 December 2022. We verified death statuses and dates from medical records and noted the cause of death with as many details as possible.

### Statistical analysis

As a univariate approach, we used the Kaplan-Meier method to plot mortality rates of detailed comorbidities.

As a multivariate approach, we used the Cox regression to estimate the HR of each comorbidity. For statistical reasons (small sample bias, calculation convergence), we had to exclude comorbidities with extreme prevalences. We set these extreme values to <2.5% and >97.5% to only consider comorbidities with at least 10 patients affected.

To limit correlations and extreme prevalences, we had to use simplified categories: 'diabetes' for diabetes whether complicated/not, 'liver disease' for severe/mild liver disease, 'neoplasia' for solid cancer/leukaemia/lymphomas. Similarly, all cardiovascular-related issues like high blood pressure, stroke, myocardial infarction, cardiac disease and lower extremity endarteritis disease got clubbed into one category.

### Evaluation of the model

We assessed the relevance of our model using two approaches: statistical and clinical. Statistically, we collected some metrics about our model (likelihood ratio, validity of proportional hazards assumption); we

**Table 1** Main characteristics of study population

| Demographics | | Total | Alive | Deceased |
|---|---|---|---|---|
| Total | | 400 | 326 | 74 |
| Age | Mean (±SD), years | 62.1 (±14.2) | 61.5 (±13.6) | 70.8 (±13.8) |
| | Median (IQR), years | 65 (53–73) | 62 (52–72) | 73 (63.25–80.75) |
| Female, n (%) | | 300 (75) | 250 (76.7) | 50 (67.6) |
| **Number of comorbidities** | | | | |
| | Mean, ±SD | 2.2±1.5 | 2±1.6 | 3±1.4 |
| | Median (IQR) | 2 (1–3) | 2 (1–3) | 3 (2–4) |
| **Number of treatments taken daily** | | | | |
| | Mean (±SD) | 5.3 (±3.7) | 4.7 (±3.5) | 8.1 (±3.6) |
| | Median | 5 | 4 | 5 |
| **Organs involved** | | | | |
| | Skins and joints, n (%) | 400 (100) | 326 (100) | 74 (100) |
| | Digestive system, n (%) | 250 (62.5) | 200 (61.3) | 50 (67.6) |
| | Heart or PAHT, n (%) | 54 (13.5) | 28 (8.8) | 26 (35.1) |
| | Lungs, n (%) | 149 (37.3) | 103 (31.6) | 46 (62.2) |
| | Kidney, n (%) | 17 (4.3) | 11 (3.4) | 6 (8.1) |

PAHT : Pulmonary Arterial HyperTension

performed again our calculations with another algorithm, a parametric one, the Weibull AFT model (Accelerated Failure Time); and we conducted a cross-validation test. We divided the database in six parts and trained the model six times on 5 of the 6 parts of the data, using the last 6th for validation.

Clinically, we used our final model to assess the HR on random patients of our dataset, to verify that our HRs were clinically relevant.

The process for preparing and analysing data to develop the SSc comorbidome is detailed in the online supplemental materials.

Please note that all associated codes are publicly available online.

## RESULTS

### Study population

A total of 454 subjects were initially eligible for our study. However, we had to exclude 54 of them; 27 did not meet the 2013 ACR/EULAR criteria, and another 27 had an excessive amount of missing data in their medical records. Thus, 400 subjects were finally included in the study, with their primary characteristics summarised in table 1. The majority of our study population comprised women (75%), having a mean age of 62.1 years (SD=14.2, from 23 to 91 years old). The average follow-up duration was 8.6 years. By the end of our observation, 18.5% (74) of the subjects had passed away.

We were able to ascertain the cause of death for 46 of these patients, the majority of which were either due to infections or neoplasms (respectively 14 and 10). 25% (11 patients) had deaths directly associated with SSc. Breakdown of the deaths attributable to SSc includes one due to acute kidney injury, five because of cardiomyopathies and pulmonary hypertension, four due to ILD, and one patient's deteriorated general health status was due to malnutrition resulting from complications linked to lower digestive tract involvement and chronic intestinal pseudo-obstruction (the patient was on parenteral nutrition) (table 2).

Most patients recorded skin and joint involvement, with the lungs and digestive tract being the next most frequently affected organs. In relation to mortality, patients with heart involvement experienced the highest death rate, followed by lung and kidney (table 1).

**Table 2** Causes of death in the subjects of our cohort

| | | |
|---|---|---|
| All | | 74 |
| | No evident cause* (%) | 28 (38) |
| | Known cause† (%) | 46 (62) |
| | SSc | 11 (15) |
| | Respiratory (non-specified) | 2 (3) |
| | Digestive | 1 (1) |
| | Infections | 14 (19) |
| | Neoplasms | 10 (14) |
| | Cardiovascular | 8 (11) |

% denotes percentage of total deaths.
*No cause specified in the medical record.
†When death occurred in our centre, we had access to the medical information.
SSc, systemic sclerosis.

**Table 3** Details of the causes of cardiopathies in our cohort

| | | |
|---|---|---|
| All | | 92 |
| SSc specific | | 54 |
| Other causes | All | 65 |
| | Rhythmic | 39 |
| | Coronary artery disease | 16 |
| | Valvulopathy | 21 |
| | Other (myocardiopathy, hypertensive cardiopathy…) | 5 |

SSc, systemic sclerosis.

## Comorbidities

We examined 14 comorbidities within this cohort. Concerning obesity, we had a substantial number of missing data, of more than >50%. Because of this and to avoid any statistical bias we chose to exclude obesity of the subsequent analysis. For all the other comorbidities, all data were available on each patient's medical record and thus used in our analysis.

For cardiovascular comorbidities, it was sometimes difficult to differentiate SSc-specific cardiac involvement and other heart disease. Patients who were only known to have specific involvement were not included in the comorbidity group (table 3).

Our patients had on average 2.2 (±1.5) comorbidities (ranging from 1 to 6), people who had died seemed to have more (3±1.4) than survivors (2±1.6). For polypharmacy, our patients took on average 5.3 (±3.7) medications daily, and deceased patients also seemed to have a bigger prescription sheet with an average of 8.1 (±3.6) (table 1).

Table 4 provides data on the prevalence and mortality rates of comorbidities. The most common conditions were polypharmacy, tobacco use and cardiovascular comorbidities, each affecting over 30% of our patients. HIV and hemiplegia occurred in less than 2.5% of cases, CTD occurred in more than 97.5%, those three were excluded from multivariate analysis. Regarding mortality, dementia, chronic kidney disease, neoplasia, polypharmacy, cardiovascular diseases and osteoporosis were the comorbidities resulting in the highest death rates, each exceeding 30%.

## Mortality

### Survival curves with Kaplan-Meier

We first plotted each binary comorbidity independently with the Kaplan-Meier. We can see in figure 1, for each comorbidity, the survival probability plotted over time based on our data (follow-up, death event) for patients having the comorbidity versus not having the comorbidity. We can see, for instance, that cardiovascular-specific involvement cumulates a high probability of death over time (0.4 after 16 years). The comorbidities are grouped thematically to enhance readability.

### Multivariate survival analysis with Cox proportional hazards model

We used a multivariate approach to study and measure the impact of comorbidities on mortality (figure 2). The

**Table 4** Mortality according to comorbidity

| Comorbidity | Patient (n) | Prevalence (%) | Deceased (n) | Deceased (%) |
|---|---|---|---|---|
| HIV* | 1 | 0.25 | 0 | 0 |
| Dementia | 11 | 2.75 | 5 | 45.45 |
| Diabetes | 17 | 4.25 | 1 | 5.88 |
| COPD† | 20 | 5 | 8 | 40 |
| Gastric ulcer | 25 | 6.25 | 5 | 20 |
| CKD‡ | 33 | 8.25 | 13 | 39.39 |
| Liver disease | 44 | 11 | 7 | 15.91 |
| Obesity | 54 | 13.5 | 4 | 7.41 |
| Osteoporosis | 56 | 14 | 18 | 32.14 |
| Neoplasia | 76 | 19 | 28 | 36.84 |
| Anxiety | 95 | 23.75 | 21 | 22.11 |
| Cardiovascular comorbidities | 177 | 44.25 | 59 | 33.33 |
| Tobacco use | 155 | 38.75 | 28 | 18.06 |
| Polypharmacy§ | 203 | 50.75 | 62 | 30.54 |

n denotes total number.
*infection by the Human Immunodeficiency Virus.
† Chronic Obstructive Pulmonary Disease.
‡ Chronic Kidney Disease.
§defined as a discrete variable, more than 4 medications.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

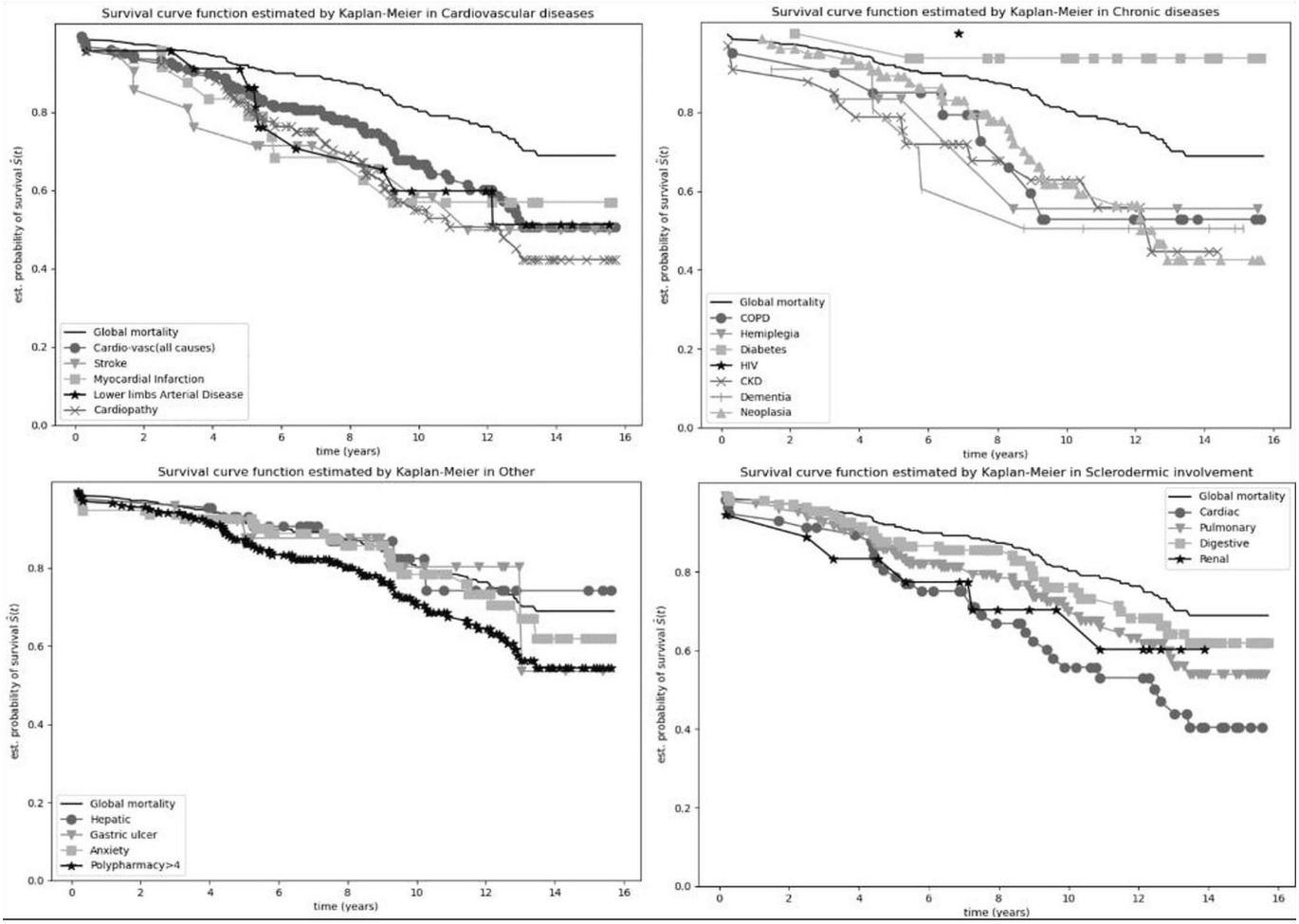


**Figure 1** Survival curves of each comorbidity using Kaplan-Meier model. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

observed associations indicate that neoplasia (HR=2.572 (1.56–4.22), p=0.0002), SSc-ILD (HR=2.45 (1.50–4.00), p=0.000), SSc cardiac involvement (HR=2.02 (1.13–3.60)), polypharmacy (HR=1.15 (1.07–1.24), p=0.0002), cardiovascular comorbidities (HR=2.02 (1.13–3.62), p=0.018) and age (HR=1.02 (1.00–1.05), p=0.044) are all significantly linked to an elevated risk of death in patients with SSc. In contrast, diabetes was associated with a reduced mortality (HR=0.05 (0.006–0.40), p=0.004) in our study.

## Evaluation of the model

We achieved a concordance index of 0.83. This indicates that HRs agree with the survival duration of patients included in the model at a rate of 83%.

The proportional hazards assumption test yielded a p value of 4.41e-14, demonstrating a high statistical significance (p<0.05) for our model.

The cross-validation test showed an accuracy rate of 76%, indicating that the model accurately predicted unknown data in 76% of instances.

For the clinical evaluation, we applied our final model to 30 patients randomly selected in the database. If we check the HR of a patient, its value reflects the survival function. A value <1 means a profile associated with better survival, and >1 means a profile associated with mortality. If we look at the smallest value (HR=0.106) associated with the best survival, we have a 22-year-old woman with no comorbidities. On the opposite, the highest (HR=12.912) corresponds to a 79-year-old woman taking 15 medications, with a gastric ulcer and a cardiovascular disease, and with lung involvement of her SSc. Patients with an HR <1 take an average of 2.6 medications, and on the other hand, patients with an HR >1 take an average of 7.7 medications. This means that with our model, polypharmacy is associated with a bigger chance of mortality. A table illustrating this process is available in online supplemental materials table 5.

## The SSc comorbidome

We formulated a comorbidome for SSc using the results obtained from our study. This representation takes the form of a bubble chart, with each comorbidity depicted as a circle. The circle's diameter represents the prevalence of the comorbidity, meaning a larger diameter corresponds to a higher prevalence. The chart's centre signifies the highest mortality rate (1/HR=0), and each comorbidity is placed accordingly, at a distance

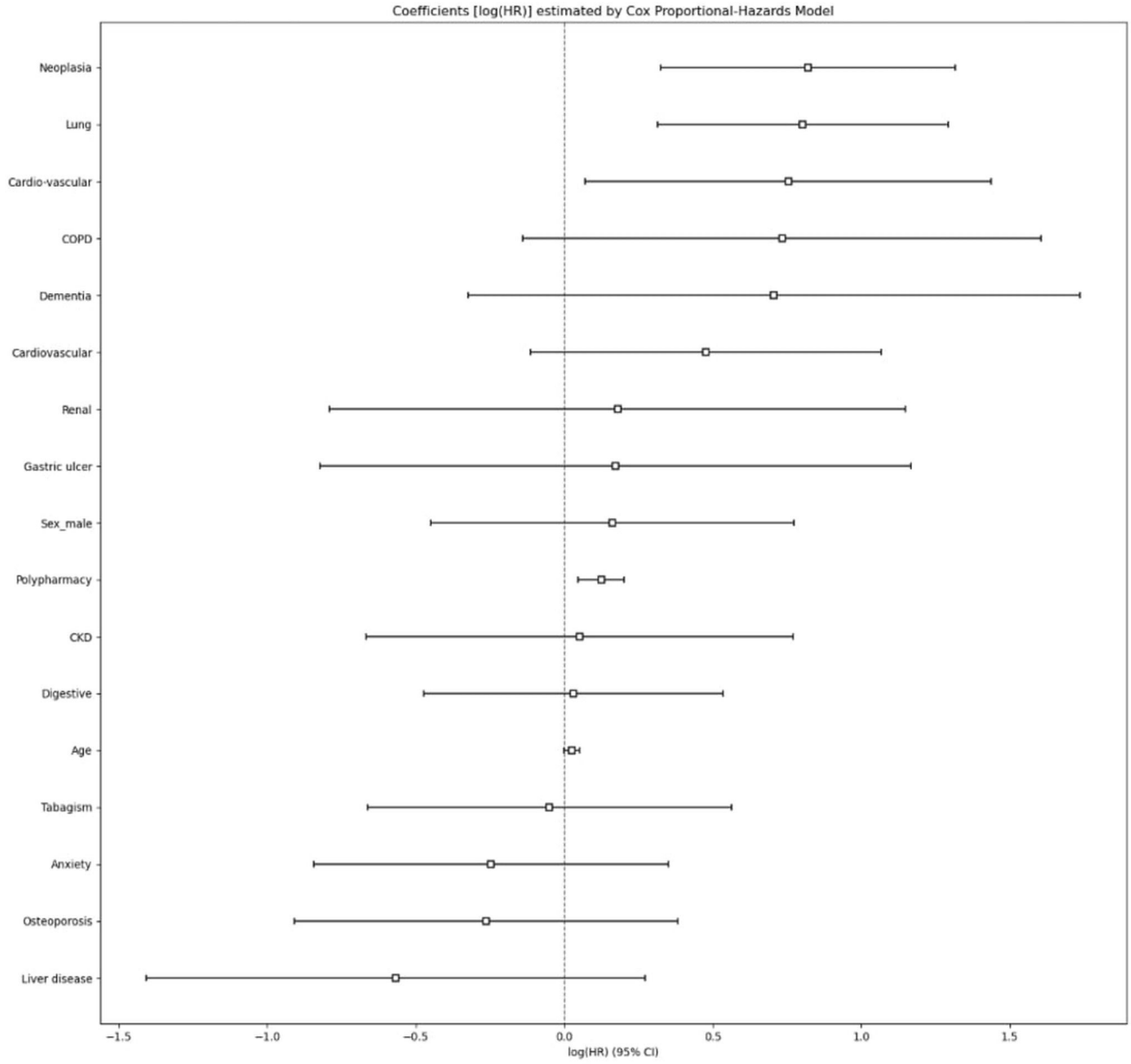


**Figure 2** Adjusted HR for death for each comorbidity and systemic sclerosis (SSc) organ involvement. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

proportional to the inverse of the HR (1/log(HR)). If comorbidity is situated closer to the centre, it signifies a higher risk of death. Among the comorbidities we studied, three displayed a statistically significant risk of death and were marked with a star for easy identification. Considering age, sex and SSc organ involvement, along with the comorbidities, enriched our model. The comorbidome effectively summarises these factors, enables a comparison between them and illuminates their reciprocal influences (figure 3).

## DISCUSSION

In this study, we conducted a retrospective observational review of patients with SSc at a specialised centre, marking the first presentation of the SSc comorbidome.[18] We examined the comorbidities these patients experienced and the impact on their mortality rate. Our multivariate analysis revealed a significant correlation between increased mortality and conditions such as neoplasia (combining solid malignant tumours, lymphoma and leukaemia), polypharmacy (defined as a continuous variable) and cardiovascular comorbidities.

The primary limitation of our study was its retrospective, monocentric design. Additionally, our study sample size, while not small for an SSc study, may not have been large enough to reveal all possible associations. Despite this, our cohort appears representative of those in existing literature, with a female-to-male ratio of 3:1, diagnosis primarily made in their fifth decade[1] and organ involvement trends that align with those of previous studies. The

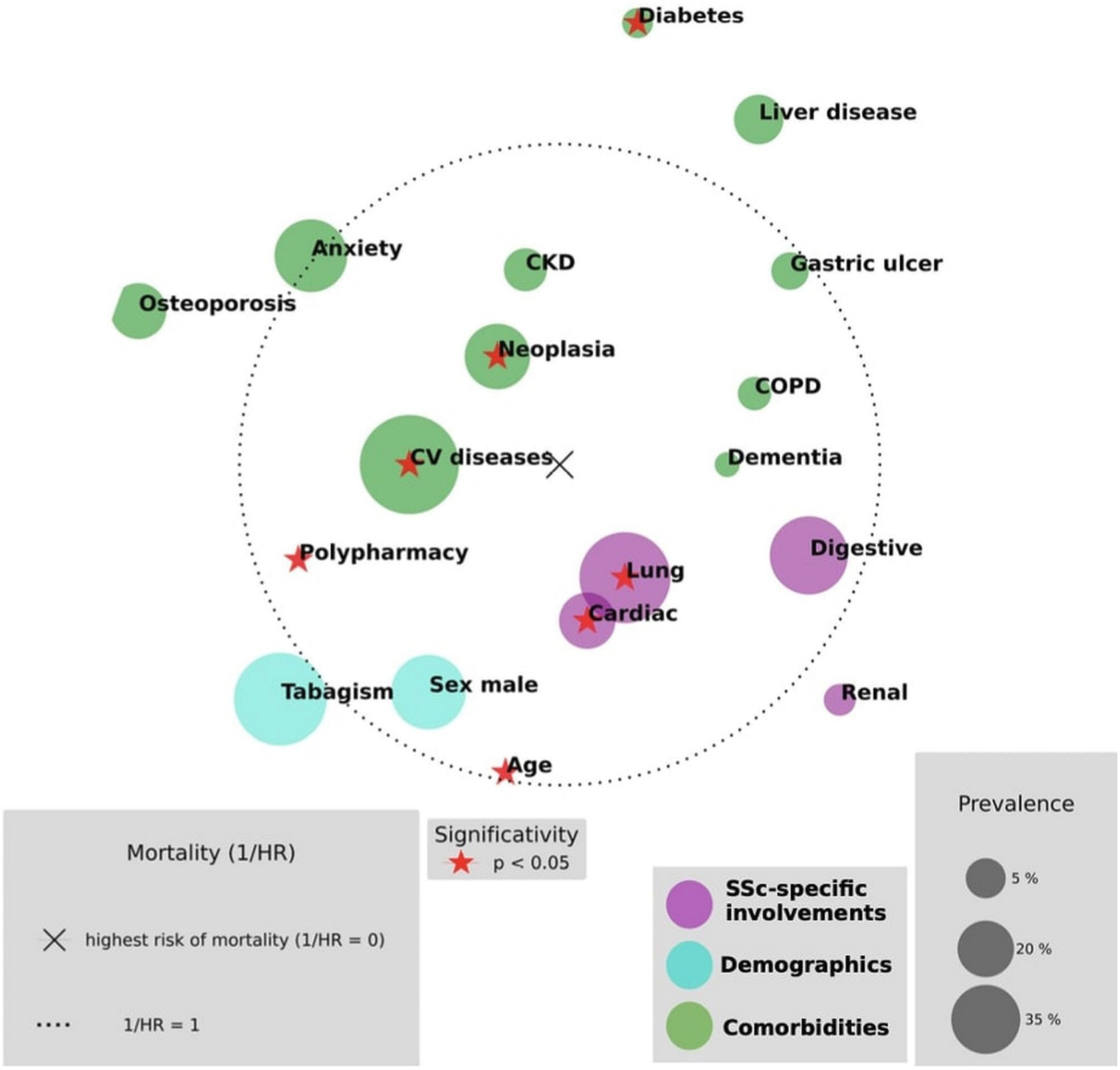


**Figure 3** Comorbidome of systemic sclerosis (SSc). The comorbidome is the graphic illustration of all the comorbidities studied in our cohort (one comorbidity=one circle), their prevalence (represented by the diameter of the circle) and their association with mortality in our patients with SSc (represented by the distance between the grey cross and the centre of the circle). All the comorbidities within the dotted circle are associated with a higher risk of death. All the comorbidities with a red star have a statistically significant association with an increased or decreased risk of death in our analysis. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

frequency of ILD as the third most common and as one of the two deadliest complications mirrors past research findings.[5] Our study's mortality causes also align with those of other studies, contributing to the generalisability of our results. Notably, however, our study reported more non-SSc-related deaths and a higher prevalence of deaths due to infectious causes compared with prior research.

This limitations may explain some counterintuitive result such as diabetes being significantly associated with survival, which has never been described. The primary issue with diabetes was its low variance, as only one death was observed in this group, which included 17 patients. This raised concerns regarding a potential sampling effect on mortality for this comorbidity, as the limited sample size may reduce the statistical power.

The well-established epidemiological and pathophysiological linkage between cancers and SSc is widely recognised. SSc can sometimes be seen as a paraneoplastic syndrome, with malignant tumours directly eliciting auto-antibody production.[19] In France, according to Santé Publique France, cancers are the leading cause of mortality, accounting for more that 26% of deaths, with cardiovascular diseases coming in second. Cancer is one of the leading causes of death in our patients, only

surpassed by infectious diseases and SSc-related complications. Showing that even though patients with SSc seem to die mainly from their disease or maybe complications of its treatment, cancers and cardiovascular diseases, as in the general population, remain of interest in the screening and management.[4]

In our study, a significant association between cancer and mortality rates was observed, with cancer also being one of the most common comorbidities. While a standard screening strategy could reduce mortality, its implementation is challenging due to the diverse clinical presentation of cancer. The specialist's discretion in prescribing additional tests is likely necessary. We opted not to differentiate solid tumours and blood cancers in our study. This decision was primarily due to the insufficient number of subjects with lymphoma or leukaemia, which would have hindered statistical analysis. Other CTDs like SLE and RA seem to have a higher incidence of blood cancers compared with solid tumours within the general population, particularly lymphomas.[20] In contrast, solid cancers[21] are more commonly linked with SSc, as was also observed in our study.

We found polypharmacy to be associated with lower survival: for each additional treatment, the mortality of our patients significantly increased. It is the first time such a result was found in SSc. Polypharmacy is a problem mainly discussed in the geriatric field and is known to increase the risk of complications in older patients.[22] Few studies focused on this problem in CTDs. Patients with SSc are often younger, but have a chronic disease, and as they get older, the number of treatments prescribed increases. It thus seemed important to us to evaluate this issue. We chose to define polypharmacy in two different ways. First, as a discrete variable (>4 treatments prescribed: yes or no) permitting us to evaluate the prevalence of this comorbidity, and it appeared to be the most frequent comorbidity in our cohort (more than 50% of our patients); with this definition, however, we did not find a significantly increased risk of death. But defined as a continuous variable (each treatment prescribed representing a new risk factor), polypharmacy was significantly associated with mortality. It is to be noted that the mean number of treatments taken by our subjects was over the standard definition for polypharmacy. Such a result underlines the frailty of these patients. More recently, the terms of problematic polypharmacy were introduced with the notion of appropriate and problematic polypharmacy (when the intended benefit of the treatment is not realised).[23] These notions go along with our result and should encourage the specialist to evaluate the complete prescription sheet at each visit.

Cardiovascular diseases are more prevalent in patients with CTDs than in the general population. This is particularly evident in cases of RA, where early atherosclerosis, commonly linked to chronic inflammation, is well documented as an inflammatory process.[6] Similarly, both cardiovascular diseases and mortality rates appear to be higher in patients with SLE, even though the underlying causes are not fully understood.[24] Past studies have also identified this increased risk in patients with SSc.[9] Besides the disease's specific microvascular involvement, these patients also seem to develop atherosclerotic plaques faster. In our study, cardiovascular comorbidities were significantly associated with mortality when viewed collectively. However, we did not find any significant correlation when we examined each comorbidity independently, possibly due to the small sample size.

The study of omics is garnering increasing interest within the scientific and medical communities as it provides a comprehensive view of a medical problem. It now enables us to understand the expression of an individual's genes and proteins or those associated with a disease (genomic, proteomic). In alignment with this, Divo *et al* started the concept of the COPD comorbidome in 2012,[8] which brought about questions related to comorbidities in this area. They brought a new method to concisely illustrate the associations between a specific disease, as SSc, patients' comorbidities and mortality, thereby providing clinicians with a more thorough understanding of the pathologies to screen in their patients.

Analysing comorbidities through the comorbidome integrates in one equation the complexity of all comorbidities or other aspects of the patient. This tool synthesises it in one value, the HR, which could be the 'comorbidities severity signature'.

Recently, this concept was borrowed for other purposes, keeping only on the comorbidome graphic representation. For instance, Buja *et al* used it to perform a comparative study of comorbidities between patients with psoriasis and controls, with no assessment of mortality.[25] We tried here to keep the initial idea of the concept, which does not necessarily need a comparison between groups, but just a comorbidities profile and a mortality rate. We kept in mind that the purpose is to offer the clinician a way to better assess their patients in a context of fragility.

Naturally, our findings require validation in a larger cohort to confirm and refine their accuracy, especially those that have raised questions. To ease this validation and possibly enable further studies in the field of comorbidities and the development of other comorbidomes, we have made our entire creation process available to the public for free online (online supplemental data).

Comparing our results in a larger cohort could also allow the creation of a mortality score, as Divo *et al* did with the COTE index, providing a more direct representation of the association between comorbidity and mortality. As increasingly aggressive treatments, such as stem cell transplants,[26] are being used in patients with SSc, the development of such a score would aid in the better selection of suitable candidates, particularly for future studies.

In conclusion, our study found a link between neoplasia (solid or haematological) and mortality in patients with SSc—a connection that has been previously identified. While it is challenging to recommend systematic screening measures based on this outcome,

specialists should be aware of the increased risk for these patients. Polypharmacy emerged as one of the most prevalent comorbidities, highlighting the fragility of these patients. Moreover, for the first time, it was identified as a mortality risk factor in SSc. This finding should prompt physicians to reassess their patients' medication lists and the benefits each drug provides. To affirm our findings, a larger cohort is crucial. Additionally, our publicised method should be employed to validate the SSc comorbidity profile.

**Contributors** Conceptualisation and study design: TF, DB, EL, JS, JC, SS, PD, EB, CC-B, TB, M-ET. Data acquisition and analysis: TF, DB, TB, M-ET. Data interpretation: TF, DB, TB, M-ET. Writing the manuscript: TF, DB, M-ET. Guarantor: M-ET. All authors read and approved the manuscript.

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**Data availability statement** We state that data (deidentified participant data) are available upon reasonable request. Statistical code is available in a public, open access repository.



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