Received: 14 February 2023 | Accepted: 26 May 2023

Rheumatology & Autoimmunity

DOI: 10.1002/rai2.12080

ORIGINAL ARTICLE

Causes and predictors of mortality in South Africans with systemic sclerosis

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Funding information
None

Abstract

Background: There is a dearth of mortality data on systemic sclerosis (SSc) in sub-Saharan Africa. We undertook a retrospective study of causes and predictors of death in low-income indigent South Africans with SSc.

Methods: A retrospective records review of clinicodemographic, laboratory, and outcome data of SSc patients attending a state-funded tertiary Rheumatology service in South Africa.

Results: Most of the 164 patients were Black (92.7%) and female (87.8%). The mean (SD) age at diagnosis and follow-up duration were 42.6 (12.9) and 5.5 (5.6) years, respectively. The majority (75.6%) had diffuse cutaneous SSc (dcSSc); and digital pits/ulcers, interstitial lung disease (ILD), and pulmonary hypertension (PH) were documented in 73.6%, 55.0%, and 38.3%, respectively. There were 56 known deaths and an equal number of patients were lost to follow-up. Deaths resulted from ILD complicated by PH (42.9%), infections (8.9%), cardiac disease (7.1%), and malignancies (3.6%). Estimated 5- and 10-year survival rates for patients with known outcomes were 58% and 42%, respectively. Independent predictors of death were renal dysfunction and cor pulmonale.

Conclusion: Most patients in this study of South Africans had dcSSc and poor outcomes. Known deaths resulted from cardiorespiratory complications of ILD complicated by PH. Cor pulmonale and renal dysfunction were independent predictors of death.

KEYWORDS

Africa, interstitial lung disease, mortality, pulmonary hypertension, systemic sclerosis

Key points

- Systemic sclerosis carries a poor prognosis in South African systemic sclerosis patients and an estimated overall 5-year survival rate of 58%.
- Cardiorespiratory complications of interstitial lung disease with or without pulmonary hypertension were the most common cause of death.
- Cor pulmonale and renal dysfunction were independent predictors of death.

1 | INTRODUCTION

Systemic sclerosis (SSc) is a rare complex multisystem autoimmune disorder characterized by vasculopathy, fibrosis, and inflammation of the skin and internal organs.[1] Known to occur in all populations, the prevalence and severity of SSc vary in different populations.[2] Of the two major subsets, namely, diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), dcSSc is more common in African and Asian patients and generally carries a worse prognosis compared to lcSSc, which is the dominant subset in Caucasians and has a more indolent course.[3,4] Moreover, interstitial lung disease (ILD) complicated by pulmonary hypertension (PH) is the major cause of morbidity and mortality in dcSSc, whereas pulmonary

arterial hypertension (PAH) is a late feature and often fatal complication in lcSSc.[5]

Overall survival in SSc has improved over the last three to four decades, but mortality remains substantially higher than that in the general population.[6] Unlike in the past when scleroderma renal crisis (SRC) was the main cause of death, ILD is now the leading cause of death.[7,8] Furthermore, studies from the United States show that outcomes in African Americans are worse compared to Caucasians,[4] at least in part due to dcSSc being more common in African Americans[4,9]

SSc has been increasingly reported in Africans,[3] and like in African Americans and Asians, dcSSc is the predominant subset.[10,11] A recent systematic review of 1668 African SSc patients showed that almost three-quarters had dcSSc and ILD reported in half the patients.[3] We have previously reported the burden of lung disease in South Africans with SSc.[12]

To date, there are no published data on causes and mortality outcomes in SSc patients in sub-Saharan Africa generally, and specifically in South Africa. Hence, we undertook a retrospective study to investigate causes and predictors of mortality in South African patients with SSc attending a state-funded tertiary care facility. Patients are mostly in either low-paid jobs or unemployed and cannot afford private health care. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Approval number: M150327).

2 | PATIENTS AND METHODS

A retrospective records review of patients with SSc attending a tertiary Connective Tissue Disease Clinic, Gauteng, South Africa between January 1, 1990 and December 31, 2015. Patients attending the service are mostly indigent, have a low household income, and depend on state-funded health services. Patients included were ≥18 years of age at first diagnosis, fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc,[13] and had ≥2 clinic visits and ≥6 months follow-up. Patients with overlap syndromes and/or inadequate clinical records were excluded from the study.

Data abstracted from case records included demographics of age, sex, and ethnicity, SSc subset of either dcSSc or LcSSc,[14] and other clinical and serological features and drug therapy. Clinical features that were recorded included Raynaud's phenomenon, digital pits/ulcers, digital gangrene, telangiectasia, calcinosis, inflammatory arthritis, joint contractures, tendon friction rubs, and inflammatory myositis, as defined by Bohan and Peter's criteria[15] and ILD. The latter was defined as clinical evidence of typical bibasal velcro-type crackles and/or evidence of interstitial infiltrate and/or the presence of honeycombing and scarring on high-resolution computed tomography (HRCT). A forced expiratory volume in 1 s (FEV1) ≤ 70% of predicted and diffusing capacity of lungs for carbon monoxide (DLCO) ≤ 60% of predicted, respectively, were used to define moderate-to-severe reductions of these lung function tests.[16] PH was diagnosed based on an estimated resting right ventricular systolic pressure >40 mmHg by transthoracic echocardiography (TTE). Serositis was defined as pleural effusion observed on chest X-ray and/or HRCT, and pericardial effusion detected by TTE.

Gastrointestinal (GI) features of heartburn, regurgitation, dysphagia, esophagitis and diarrhea, constipation, malabsorption, and abdominal pain or distension were aggregated as upper and lower GI features, respectively. Proteinuria of ≥1+ on urine dipstick testing was considered abnormal and a serum creatinine >110 mmol/L was defined as renal dysfunction. SRC was defined as rapidly progressive renal failure, usually high blood pressure, high creatinine, proteinuria, and microscopic hematuria.[17]

Autoantibody data included antinuclear antibodies (ANAs) and anticentromere antibodies (ACAs) detected by indirect immunofluorescence using Hep2 cells as substrate. Antibodies to extractable antigens, Sm, U1RNP, Ro, and La antibodies were detected by enzyme-linked immunosorbent assay and antitopoisomerase-1 (ATA) and anti-Jo-1 antibodies by Western blotting assays.

Causes of death were ascertained from clinical records review, hospital mortuary registers, and the National Department of Home Affairs database of reported deaths. Outcomes were categorized as the known alive (AG), known deceased (DG), and lost to follow-up (LG) groups. Deaths were classified as directly related or unrelated to SSc.

2.1 | Statistical methods

Student's *t*-test and χ^2 test/Fisher's two-tailed exact test were applied to compare continuous and categorical variables, respectively, between groups. Odds ratios with a 95% confidence interval were calculated for categorical variables. Survival curves and estimates were computed with Kaplan–Meier analysis. Univariate and multivariate Cox proportional hazard regression tests were used to determine predictors of death. Only variables with a $P < 0.15$ in the univariate analysis were included in the stepwise multivariate regression analysis. A $P < 0.05$ was deemed to be statistically significant. All statistical analyses were performed using MedCalc® Statistical Software version 20.11 (MedCalc Software; https://www.medcalc.org).

3 | RESULTS

A total of 291 case records were reviewed. Of these, 282 patients met the 2013 ACR/EULAR classification criteria for SSc. A further 118 were excluded because of failure to meet either the inclusion criteria of follow-up duration ≥6 months and/or exclusion criteria of overlapping clinical features and inadequate recorded data. The remaining 164 patients included in the analysis were mostly Black (92.7%) and female (87.8%) (Table 1). The mean (SD) age at diagnosis and follow-up duration

TABLE 1 Demographics and cumulative clinical and laboratory features of 164 South Africans with systemic sclerosis.

Variables	All patients, *n* (%)	Known alive, *n* (%)	Known demised, *n* (%)	Lost to follow-up, *n* (%)	OR (95% CI)[a]	*P*
Female gender	144 (87.8)	50/52 (96.2)	49/56 (87.5)	45/56 (80.4)	0.28 (0.05–1.42)	0.16
Black ethnicity	152 (92.7)	47/52 (90.4)	54/56 (96.4)	51/56 (91.1)	2.87 (0.53–15.50)	0.26
Age of symptoms onset (years)	40.2 (13.2)	40.4 (13.2)	41.4 (13.3)	38.7 (13.3)	–	0.69
Age (SD) at diagnosis (years)	42.6 (12.9)	42.1 (12.5)	45.1 (12.2)	40.6 (13.8)	–	0.20
Follow-up duration (SD) (years)	5.5 (5.6)	8.9 (6.9)	4.1 (3.9)	3.8 (4.1)	–	<0.0001
Smoking history	22/150 (14.7)	6/48 (12.5)	4/46 (8.0)	12/52 (23.1)	0.66 (0.17–2.53)	0.74
Diffuse cutaneous disease	124 (75.6)	34/52 (65.4)	49/56 (87.5)	41 (73.2)	3.71 (1.40–9.84)	0.007
Raynaud's phenomenon	158 (96.3)	50/52 (96.2)	54/56 (96.4)	54/56 (96.4)	1.08 (0.15–7.96)	1.00
Digital lesions						
Ulcers	120/163 (73.6)	35/51 (68.6)	48/56 (85.7)	37/56 (66.1)	2.74 (1.06–7.12)	0.03
Gangrene	15/155 (9.7)	3/45 (6.7)	7/55 (12.7)	5/55 (9.1)	2.04 (0.50–8.40)	0.50
Telangiectasia	54/146 (37.0)	20/42 (47.6)	16/53 (30.2)	18/51 (35.3)	0.47 (0.20–1.10)	0.09
Calcinosis cutis	41/136 (30.1)	10/35 (28.6)	17/53 (32.1)	14/48 (29.2)	1.18 (0.46–3.00)	0.72
Inflammatory arthritis	53/162 (32.7)	15/51 (29.4)	20/56 (35.7)	18/55 (32.7)	1.33 (0.59–3.00)	0.49
Joint contractures	53/150 (35.3)	17/43 (39.5)	22/55 (40.0)	14/52 (26.9)	1.02 (0.45–2.30)	1.00
Tendon friction rubs	15/116 (12.9)	4/29 (13.8)	5/47 (10.6)	6/40 (15.0)	0.74 (0.18–3.03)	0.72
Inflammatory myopathy	35/153 (22.9)	9/48 (18.8)	12/52 (23.1)	14/53(26.4)	1.30 (0.49–3.43)	0.60
Upper GI symptoms	146/161 (90.7)	46/51 (90.2)	54/55 (98.2)	46/55 (83.6)	5.87 (0.66–52.07)	0.10
Lower GI symptoms	18/159 (11.3)	9/51 (17.6)	6/54 (11.1)	3/54 (5.6)	0.58 (0.19–1.77)	0.34
Serositis	20/160 (12.5)	3/51 (5.9)	12/55 (21.8)	5/54 (9.3)	4.47 (1.18–16.89)	0.03
Interstitial lung disease	88/160 (55.0)	29/51 (56.9)	34/54 (63.0)	25/55 (45.5)	1.28 (0.59–2.82)	0.52
FEV1 ≤ 70% baseline predicted	35/97 (36.1)	10/28 (35.7)	12/36 (33.3)	13/33 (39.4)	0.9 (0.32–2.54)	0.84
DLCO ≤ 60% baseline predicted	30/89 (33.7)	7/26 (26.9)	14/34 (41.2)	9/29 (31.0)	1.9 (0.63–5.72)	0.25
Pulmonary hypertension	59/154 (38.3)	13/50 (26.0)	31/54 (57.4)	15/50 (30.0)	3.83 (1.67–8.80)	0.001
Cor pulmonale	29/154 (18.8)	0/50 (0)	22/54 (40.7)	7/50 (14.0)	35.94 (4.62–279.36)	<0.0001
Hypertension	65/161 (40.4)	24/51 (47.1)	21/55 (38.2)	20/55 (36.4)	0.69 (0.32–1.51)	0.35
Scleroderma renal crisis	5/162 (3.1)	0/52 (0)	3/55 (5.5)	2/55 (3.6)	4 (0.43–37.01)	0.36
Proteinuria	41/152 (27.0)	13/52 (25.0)	20/51 (39.2)	8/49 (16.3)	1.94 (0.83–4.50)	0.12
Renal dysfunction	27/162 (16.7)	1/52 (1.9)	16/55 (29.1)	10/55 (18.2)	20.9 (2.66–164.64)	0.0001

Abbreviations: FEV1, forced expiratory volume in 1 s; DLCO, diffusion capacity for carbon monoxide; GI, gastrointestinal; OR (95% CI), odds ratio with 95% confidence interval.

[a]Known demised versus known alive groups.

were 42 (12.9) and 5.5 (5.6) years, respectively. Overall, there were 52 (31.8%) in the AG, 56 (34.1%) in the DG, and 56 (34.1%) in the LG (Table 2).

Most patients had dcSSc and the most common clinical features were Raynaud's phenomenon (96.3%), upper GI symptoms (90.7%), digital pits/ulcers (73.6%), and ILD (55.0%). HIV infection and tuberculosis (TB) were documented during follow-up in 11/101 (10.9%) and 10/140 (7.1%), respectively. ANA, ATA, ACA, and anti-U1RNP antibodies were positive in 90.6%, 28.3%, 8.1%, and 33.3% of patients, respectively (Figure 1). Known deaths occurred significantly more in patients with dcSSc, who also had a shorter follow-up period and were more likely to have digital ulcers. Drugs most frequently prescribed were proton pump inhibitors (78.0%), angiotensin-converting enzyme inhibitors (62.3%), and calcium channel blockers (64.0%). Corticosteroids (59.7%) were prescribed usually in doses ≤15 mg daily, except for patients with myositis or serositis in whom doses of ≤30 mg daily were prescribed. Immunomodulatory agents were prescribed overall in 54% of patients and included D-penicillamine (20.5%), azathioprine (15.5%), cyclophosphamide (26.7%), methotrexate (19.5%), and mycophenolate mofetil (3.4%). There was no significant difference in the use of immunomodulatory agents between DG and AG (Supporting Information: Table).

Thirty-one (57.1%) deaths were deemed to be disease-related, of which most, 24 (42.9%), were due to

TABLE 2 Predictors of mortality in 108 South Africans with systemic sclerosis by univariate and multivariate Cox regression analysis.

Variables	Univariate analysis HR (95% CI)	*P*	Multivariate analysis HR (95% CI)	*P*
Serositis	2.92 (1.51–5.60)	0.001	–	–
Pericardial effusion	3.03 (1.54–6.00)	0.001		
Pleural effusion	3.59 (1.41–9.14)	0.007		
Pulmonary hypertension	1.90 (1.11–3.23)	0.020		
Cor pulmonale	2.89 (1.68–4.94)	0.0001	2.20 (1.23–3.90)	0.008
Scleroderma renal crisis	4.76 (1.42–15.96)	0.010		
Proteinuria	1.75 (1.01–3.03)	0.050		
Renal dysfunction	3.86 (2.12–7.01)	<0.0001	2.85 (1.51–5.40)	0.001

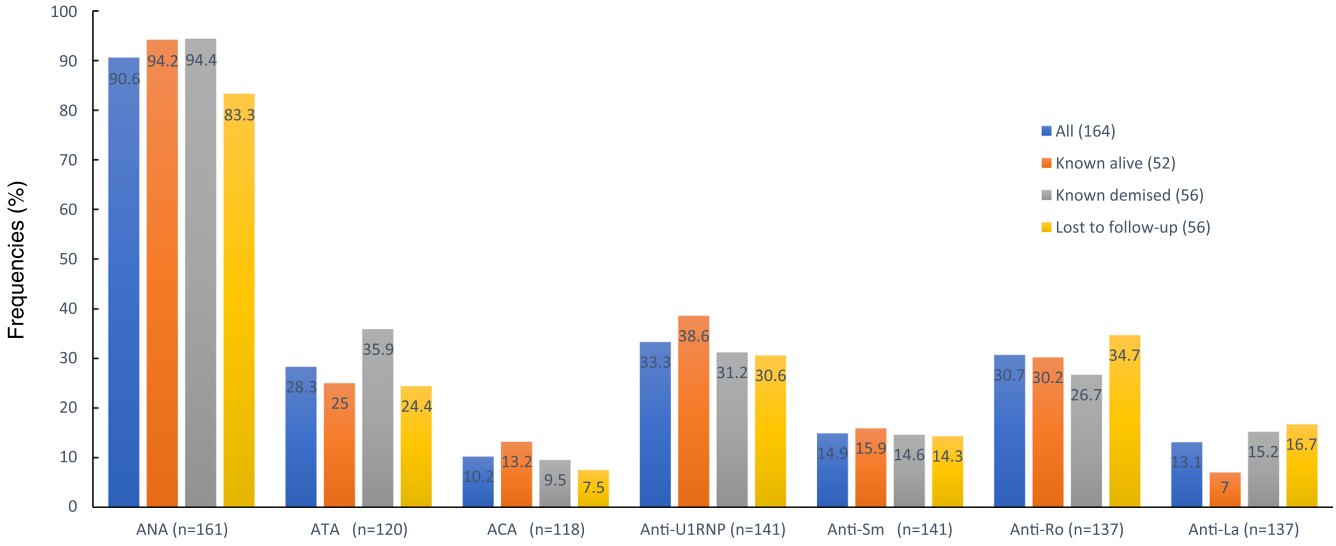

FIGURE 1 Antibody frequencies in 164 South African systemic sclerosis patients. ACA, anticentromere antibodies; ANA, antinuclear antibodies; ATA, antitopoisomerase-1.

ILD with or without PH. Other disease-related deaths were from primary cardiac disease in four (7.1%), and one each of SRC, thoracic cage collapse from advanced osteolysis,[18] and lower gut complications. Nine SSc-unrelated causes of death were due to infections (pneumonia (3), leg sepsis and septicemia (1), and septicemia (1)), solid tumors (prostate (1), lung adenocarcinoma (1)), subacute intestinal obstruction (1), and stroke (1). An exact cause of death was not established in 16 (28.8%) of patients.

Estimated overall 5- and 10-year survival rates were 58% and 42%, respectively. Univariate Cox regression analysis showed that renal dysfunction ($P < 0.0001$), serositis ($P = 0.001$), and PH ($P = 0.02$), particularly when complicated by cor pulmonale ($P = 0.0001$), SRC ($P = 0.01$), and proteinuria ($P = 0.047$) were associated with death (Figure 2). Of note, there was no significant association with ILD ($P = 0.90$), FEV1 ≤ 70% of predicted ($P = 0.80$), and DLCO ≤ 60% of predicted ($P = 0.16$). Multivariate Cox regression analysis showed only renal dysfunction and cor pulmonale [HR (95% CI) = 2.85 (1.51–5.40) and 2.20 (1.23–3.90), respectively) to be independently associated with death.

3.1 | Discussion

In this study of mostly low-income indigent Black South Africans with SSc in whom dcSSc was the predominant subset, there was a high burden of cardiorespiratory complications and associated mortality. These findings are consistent with US studies where dcSSc is common in African Americans and cardiorespiratory complications are a major challenge in patients with dcSSc.[4,9]

Most deaths in the present study were disease-related, like in a large multicentre European study.[6,8] As in previous studies, ILD with or without PH/cor pulmonale was the most common disease-related cause of death. We previously found that 40% of SSc patients with moderate-to-severe ILD did poorly despite treatment with immunosuppressive agents including cyclophosphamide and mycophenolate mofetil.[12] SRC was rarely occurring in three patients and resulting in only one death. Apart from SRC having a better outcome since the introduction of ACEi,[7] anti-RNA polymerase I/III antibodies, which are associated with SRC in Caucasians, are rare in Africans.[3,19]

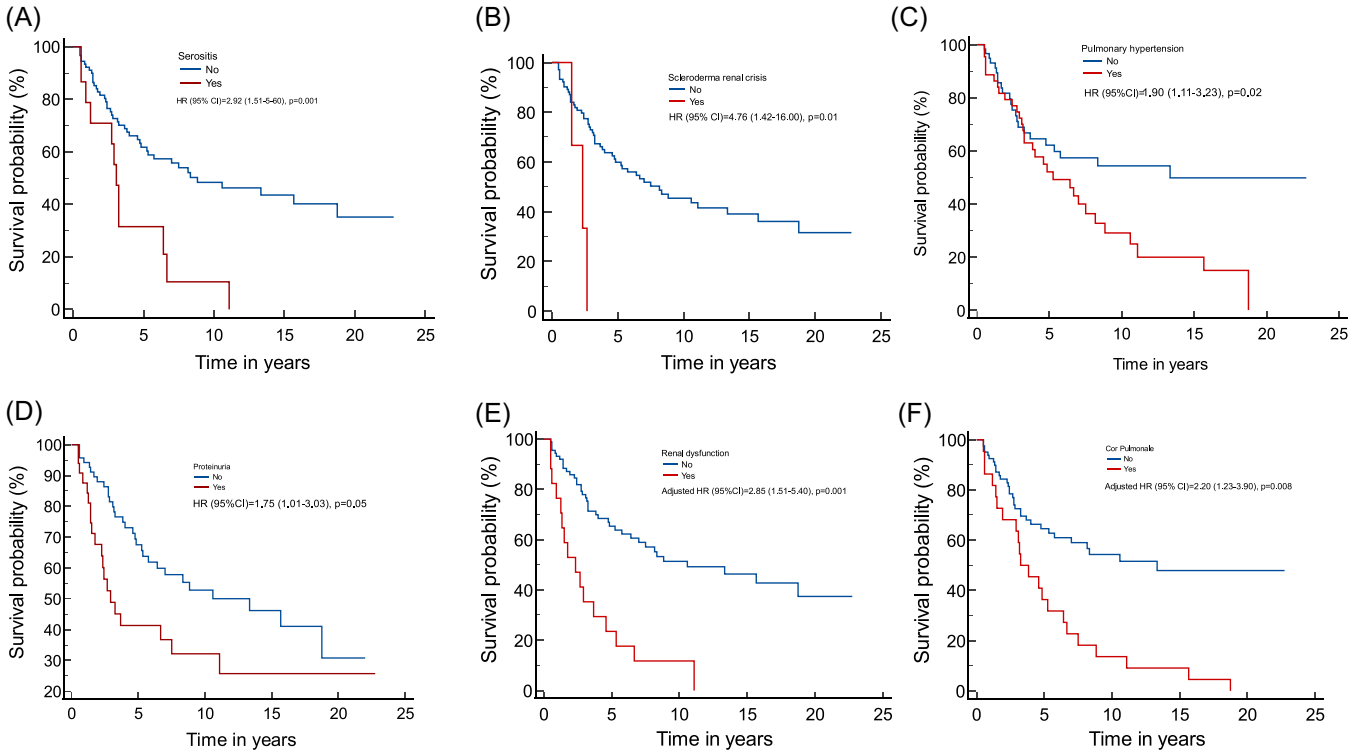

FIGURE 2 Kaplan–Meier survival curves for 164 South African systemic sclerosis patients by the presence or absence of (A) serositis, (B) scleroderma renal crisis, (C) pulmonary hypertension, (D) proteinuria, (E) cor pulmonale, and (F) renal dysfunction.

A minority of known deaths were due to infections and not related to underlying HIV and TB. This contrasts with our experience of SLE, where serious infections, especially TB, are a major cause of morbidity and mortality.[20,21] In part, this might be related to less exposure to corticosteroids and immunosuppressive drugs in SSc patients. We previously found that both the maximum dose and duration of corticosteroid therapy are risk factors for TB in our SLE patients.[21] That only two of the deaths were due to malignancies in the present study, much lower than the 13% reported in a large EUSTAR study of mainly Caucasians,[8] might reflect the younger mean age of the present cohort and shorter follow-up period compared to the EUSTAR cohort and lower prevalence of solid tumors, especially lung cancer in black women, compared to other ethnic groups in South Africa.[22]

Estimated overall 5- and 10-year survival rates of 58% and 42%, respectively, are substantially lower than observed in industrialized countries. In multiethnic studies, Caucasians have been shown to have the best survival rates. In the United States, 5-year survival rates were 85% for Caucasians compared to 76% for African Americans,[9] and 10-year survival rates as high as 92% have been reported in a Swiss study comprising mainly Caucasian patients.[23] The stark difference in survival rates reflects in part socioeconomic disparities in access to quality health care between the industrialized world and developing countries like South Africa. In addition, intrinsic biological factors play a role where the aggressive dcSSc and associated cardiorespiratory complications are more common in patients of African extraction.[2,24]

As reported previously in various populations, several clinical features were associated with an increased risk of death, including PH, serositis, proteinuria, and renal dysfunction.[8,25,26] Although ILD was common in our study, occurring in more than 50% of patients overall, it was not associated with an increased risk of death, unlike in previous larger studies.[8] Instead, we found that only when ILD was complicated by PH, and especially cor pulmonale, did it have a negative effect on survival. Serositis and renal dysfunction, the latter conferring the highest risk for death, have both been shown previously to be associated with death in Spanish and Hungarian patients.[25]

Inherent to most retrospective studies, missing data and patients lost to follow-up were major limitations. Despite our best efforts to get information from the hospital mortuary and National Department of Home Affairs database of reported deaths, we were unable to obtain information on possible deaths of patients lost to follow and precise causes of death in 28% of patients known to have died. Also, documentation of clinical features and investigations in case records varied over the years due to differing levels of clinical expertise and experience of physicians and access to special investigations such as HRCT. Similarly, the use of immunomodulatory agents changed over time: D-penicillamine was withdrawn from the hospital formulary in the early 2000s. Another change that has occurred is the greater use of mycophenolate mofetil, especially so in more recent years beyond the period of this study.

Notwithstanding these limitations, our findings provide new insights into morbidity and mortality in mainly indigent black South Africans with SSc. ILD

when complicated by PH and cor pulmonale is the major cause of death. The large proportion of patients lost to follow-up highlights challenges in long-term follow-up in the public healthcare sector of South Africa.

AUTHOR CONTRIBUTIONS

Concept/design: Zodwa Dire, Mohammed Tikly, and Claudia Ickinger. *Data collection*: Zodwa Dire. *Data analysis/interpretation*: Zodwa Dire, Mohammed Tikly, and Claudia Ickinger. *Drafting article*: Zodwa Dire and Mohammed Tikly. *Critical revision of the article*: Claudia Ickinger. *Approval of article*: Zodwa Dire, Mohammed Tikly, and Claudia Ickinger.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of the Witwatersrand (Approval number: M150327).

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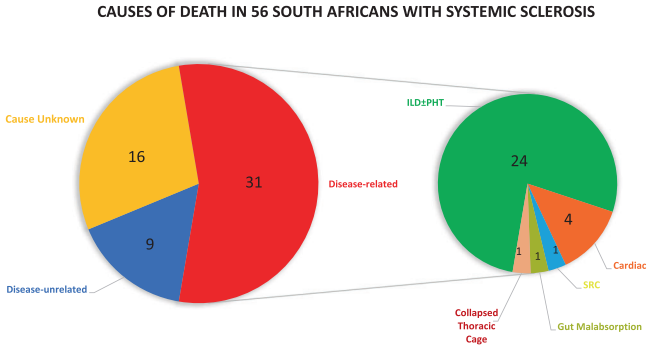
SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dire Z, Ickinger C, Tikly M. Causes and predictors of mortality in South Africans with systemic sclerosis. *Rheumatol & Autoimmun*. 2023;3:108-114. doi:10.1002/rai2.12080

GRAPHICAL ABSTRACT

This graphical abstract will be a part of HTML, Online and Print versions.



Causes of death in 56 known deaths of 164 patients in South Africa with systemic sclerosis.