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Dire, Zodwa Nwabisa

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CAUSES AND PREDICTORS OF MORTALITY IN SYSTEMIC SCLEROSIS AT A TERTIARY SOUTHERN GAUTENG HOSPITAL

Zodwa Nwabisa Dire

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 2018

DECLARATION

I, Zodwa Nwabisa Dire, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

Signed at ……..on ……. day……2018

DEDICATION

I dedicate this research report to my family; my husband, Mothusi, my children Rorisang and Gomolemo, my mother, Nondumiso and my sister Fundiswa.

LIST OF PRESENTATIONS

5TH Systemic Sclerosis World Congress 2018, Bordeaux:

Z Dire, M Tikly, C Ickinger Causes and predictors of mortality in systemic sclerosis in South Africans (poster presentation).

ABSTRACT

Background

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease primarily affecting skin and internal organs. It is characterized by excessive fibrosis, vasculopathy and chronic inflammation. The disease is associated with increased morbidity and mortality, but to date, there have been no studies on causes of death and predictors thereof in Sub-Saharan Africa.

Objective

To determine the spectrum of causes of death in SSc patients attending the Connective Tissue Disease Clinic at the Chris Hani Baragwanath Academic Hospital.

Methods

A retrospective record review of patients meeting the ACR/EULAR (full criteria attending the Connective Tissue Disease Clinic at Chris Hani Baragwanath Academic Hospital between Jan 1990 to Dec 2015).

Results

Of the 282 records reviewed, 174 patients met the inclusion criteria. The majority of patients were Black African (92.5%), with a female to male ratio of 7:1. The mean (SD) age at diagnosis and follow up period were 41.8 (13.1) years and 65.8 (66.4) months respectively at last visit. Only 53 were known to be alive at the end of the study, 63 were lost and/or could not be found during follow-up, and there were 58 known deaths. The major known causes of death were disease-related: cardiopulmonary in 24 (41.4%) and SRC in 1 patient (1.7%). The disease-unrelated causes included infection in 5 patients (8.6%) and malignancy in 2 patients (3.5%).

Predictors of mortality included serositis, renal dysfunction, digital ulcers, proteinuria, and a raised C-reactive protein (CRP). The estimated survival rates were 56.3% at 5 years and 35.8% at 10 years – censored for patients lost to follow up.

Conclusion

In the present study, SSc was associated with a high morbidity and mortality especially cardiorespiratory complications. The cause of death in our study was predominantly disease related, which is in accordance with that reported in other studies. Cardiopulmonary causes remain the leading causes of death in our population comparable to that reported in studies done in other countries.

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ABBREVIATIONS

ACA	Anti-centromere antibodies
ACEI	Angiotensin converting enzyme inhibitors
ACR	American College of Rheumatology
ANA	Antinuclear antibodies
ANOVA	Analysis of variance
Anti-DsDNA	Double stranded deoxyribonucleic acid antibodies
Anti-La	Antibodies to La protein
Anti-PmScl	Anti-Polymyositis/scleroderma antibodies
Anti-RNAP	Anti-ribonucleic acid polymerase antibodies
Anti-RNP	Anti-ribonucleoprotein antibodies
Anti-Ro	Antibodies to Ro antigen
Anti-Sm	Antibodies to Smith antigen
Anti-U3RNP	Anti-U3 ribonucleioprotein antibody
ARB	Angiotensin receptor blocker
ATA	anti-topoisomerase 1 antibodies
CK	Creatine kinase
CRP	C-reactive protein

DcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusion capacity of carbon monoxide
ECG	Electrocardiography
EMG	Electromyography
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GAVE	Gastric antral vascular ectasia
GIT	Gastrointestinal tract
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
LcSSc	Limited cutaneous systemic sclerosis
mRSS	Modified Rodnan skin score
PAH	Pulmonary arterial hypertension

PH	Pulmonary hypertension
RP	Raynaud’s phenomenon
SRC	Scleroderma renal crisis
SSc	Systemic sclerosis
TB	Tuberculosis

CHAPTER ONE: LITERATURE REVIEW

1.1 Definition

Systemic sclerosis (SSc), also known as scleroderma, is a chronic systemic autoimmune disease primarily affecting the skin and internal organs (Rodnan and Benedek 1962). It is characterized by vascular abnormalities, fibrosis, inflammation and atrophy of the skin and internal organs (Czirjak, Foeldvari et al. 2008) . In 1988, formal definitions of subsets were described. These include diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), SSc sine scleroderma, environmentally-induced SSc, and overlap syndromes (LeRoy, Black et al. 1988). Evidence of diffuse cutaneous SSc is skin thickening that extends from the digits proximally to the elbows and/or knees. This subset is more likely to be associated with systemic involvement such as renal crisis, pulmonary fibrosis and cardiomyopathy. In the case of lcSSc, skin thickening is restricted mainly to the fingers, hands and forearms, and is associated with less involvement of internal organs except for pulmonary hypertension (Meyer, Fertig et al. 2007). Systemic sclerosis sine scleroderma presents with typical organ involvement but with no clinical evidence of skin thickening (Molina, 1995).

1.2 History of systemic sclerosis

The term scleroderma is derived from the Greek word *skleros*, meaning hard or indurated, and *derma*, meaning skin (de Silva and Parish 1994). Even though a number of physicians in ancient times described patients with hardening of the skin, none of the descriptions were conclusive. The closest was a delineation by Hippocrates around 400 BC, who described an Athenian man with indurated unpinchable skin (de Silva and Parish 1994). In 1818, Alibert, a French dermatologist commented about SSc as “nothing is more bizarre, but also nothing is more interesting than corn degeneration of dermoid system” (Rodnan 1962). Dr Curzio, an Italian

doctor, subsequently published the first case report of SSc in 1753, which, to date, is considered the first definitive account of the disease. Despite there being some doubts with regards to the clinical presentation of the patient, as the clinical features disappeared after 11 months, this is still considered a landmark in the discovery and description of the disease (Roberts-Thomson and Walker 2006). Following these publications, more clinicians became aware of the condition and its clinical manifestations. Thus, several more cases were reported by the late nineteenth century physicians (de Silva and Parish 1994). The term scleroderma was later changed to progressive systemic sclerosis by a South African pathologist, Dr Goetz, who observed multi organ involvement in autopsy studies (de Silva and Parish 1994). Eventually, the term "progressive" was removed, as not all cases of SSc were necessarily progressive in nature.

1.3 Epidemiology

1.3.1 Global epidemiology

Different studies done in different countries show variation in the global occurrence of SSc. As shown in Table 1, reported prevalence rates vary widely from as low as 30.8 cases per million in England, to as high as 658,6 cases per million in the Choctaw Indians of USA (Barnes and Mayes 2012). Moreover, the prevalence rates vary by gender and race, with females being affected 4 to 5 times more than males and blacks more than whites. Generally, lcSSc is the predominant subset in Caucasians and dcSSc in other populations (Joven, Almodovar et al. 2010).

Table 1: Epidemiology of SSc (Barnes and Mayes 2012)

Epidemiology and health-related services

Table 1. Incidence and prevalence in past decades

Publication	Region	Study period	Incidence per million	Prevalence per million
USA				
Steen *et al.* [4]	Pennsylvania	1963–1972, 1973–1982, 1963–1982	13.9 (entire period)	
Maricq *et al.* [5]	South Carolina	1989	–	286
Mayes *et al.* [6]	Michigan	1989–1991	21	276
Arnett *et al.* [7]	Oklahoma	1996		658.6
Bernatsky *et al.* [8]	Quebec	2003	–	443
Australia				
Englert *et al.* [9]	Sydney	1974–1988	12	45.2 (1975) 86.2 (1988)
Chandran *et al.* [10]	South Australia	1987–1993	–	208
Roberts-Thompson *et al.* [11]	South Australia	1993	15.1	200
		1999	22.8	233
Roberts-Thompson *et al.* [12]	South Australia	1993–2002	20.4	232.2
Japan				
Tamaki *et al.* [13]	Tokyo	1987	7.2	38
UK and Europe				
Silman *et al.* [14]	England (West Midlands)	1986	3.7	31
Allock *et al.* [15]	England (Newcastle)	2000	–	88
Geirsson *et al.* [16]	Iceland	1975–1990	3.8	71
Kaipiainen-Seppanen and Aho [17]	Finland	1990	3.7	
Le Guern *et al.* [18]	France (Seine-St-Denis	2001	–	158
Alamanos *et al.* [19]	Greece (Northwest)	1981–2002	11	154
Arias-Nunez *et al.* [20]	Spain (Northwest)	1988–2006	23	277

1.3.2 Epidemiology of systemic sclerosis in Africa

There have been no formal epidemiological studies on the incidence and prevalence rates of SSc in Africa. One study in a Kinshasa health care facility reported a 0.6% of rheumatological cases seen in a rheumatology clinic (Malemba and Mbuyi-Muamba 2008).

1.3.3 Environmental risk factors

Although the exact cause(s) of SSc remain unknown, environmental risk factors contribute to the development of the disease. These risk factors are both occupational and non-occupational

related. The most well-described occupational risk factor is exposure to silica. A higher incidence has been described in gold miners with exposure to silica dust; suggesting a contribution of silica in the pathogenesis (Cowie 1987). Some studies have reported the risk of developing SSc to be 5 to 6 times higher in people exposed to silica dust compared to the general population (Dospinescu, Jones et al. 2013). There is some evidence suggesting a link between solvent exposure and early SSc development (Dospinescu, Jones et al. 2013). A study carried out in France found that individuals with high cumulative exposure to solvents were 5 times more likely to develop SSc than the general population (Marie, Gehanno et al. 2014). Other studies looking at other occupation exposures such as vibration and fumes have yielded no positive association (Dospinescu, Jones et al. 2013). Non-occupational environmental risk factors such as smoking and alcohol consumption have also been associated with a higher risk for developing SSc. Smoking is thought to have greater impact on disease severity rather than a risk factor for developing SSc (Dospinescu, Jones et al. 2013). Other environmental factors postulated as contributors to the aetiology of the disease include vinyl chloride, medications such as bleomycin, pentazocine, and cocaine, and viruses such cytomegalovirus and parvovirus B19 (Balbir-Gurman and Braun-Moscovici 2012). These chemicals and microbes are thought to cause immunologically mediated vascular injury, inflammation and tissue fibrosis; with the latter being the predominate pathological feature of SSc (Saketkoo, Magnus et al. 2014).

1.4 Genetics risk factors

Genetic risk factors appear to play less of a role in predisposing SSc compared to other connective tissue diseases. Twin studies have shown a poor concordance with disease expression but better concordance with autoantibodies (Feghali-Bostwick, Medsger et al. 2003). Even though positive family history is still regarded as one of the strongest genetic risk factor, the

actual familial risk is very low (Herrick and Worthington 2002). The highest incidence of SSc has been documented in the Choctaw Indians of North America (Table 1), and is due to a unique HLA haplotype (include haplotype) (Arnett, Howard et al. 1996). Like in other autoimmune connective tissue diseases,,SSc has been associated with certain HLA class II antigens. Principally, HLA DR3 occur more frequently in Caucasion with lcSSc, and HLA DR15 with dcSSc in other populations including South Africans (Tikly, Rands et al. 2004). A number of non-HLA genes are also known to be associated with scleroderma in Caucasian populations.

1.5 Aetiopathogenesis

Although the precise aetiology of the disease remains elusive, there are several lines of evidence suggesting that environmental factors in a genetically susceptible host triggers the disease process leading to initially vascular abnormalities, followed by immune-mediated chronic inflammation and fibrosis of the skin and visceral organs (Charles, Clements et al. 2006)

1.6 Clinical features and classification criteria

1.6.1 Clinical features

Systemic sclerosis has a variable presentation. In patients with DcSSc, there is extensive skin involvement and frequent internal organ fibrosis such as interstitial lung disease on the other hand in patients with LcSSc, vascular features such as RP or telangiectasia and pulmonary arterial hypertension predominate. Whereas LcSSc is the predominate subset in Caucasians, DcSSc is seen more often in other populations including Africans (Laing, Gillespie et al. 1997, Tager and Tikly 1999).The age of onset is generally lower in DcSSc compared to LcSSc (Steen, Domsic et al. 2012).

The most common clinical manifestation of SSc is Raynaud's phenomenon (RP), with more than 90% of patients reported to have RP at presentation (Meier, Frommer et al. 2012). It symbolizes one of the early signs of presentation of the disease. With time, RP can progress to an exaggerated form of vasculopathy, presenting in the form of digital ulcers and digital gangrene.

Cutaneous manifestations are characterized by skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints limited to the elbow and knees in LcSSc and extending beyond the elbows and knees in dcSSc. Oher manifestations include ("salt and pepper pigmentation"), telangiectasia, calcinosis, hypo and hyperpigmentation and nailfold capillary changes. The modified Rodnan skin score (mRSS), which looks at the degree of skin thickening at different sites of the body, is used as a measure of the extent and severity of skin involvement.

The gastrointestinal manifestations of the disease are common, with most studies reporting a frequency of more than 60% (Hesselstrand, Scheja et al. 1998, Meier, Frommer et al. 2012, Poormoghim, Moghadam et al. 2013). The disease can affect any part of the gastrointestinal tract from the oral cavity to the anus. Dysphagia and reflux are the commonest early symptoms. In established cases, patients might develop malabsorption and faecal incontinence.(Tian and Zhang 2013).

Renal manifestations are rare and vary from asymptomatic proteinuria to a severe complication like scleroderma renal crisis (SRC), which in a recent study, has been reported to have a frequency of 2.1% (Meier, Frommer et al. 2012). Mortality related to SRC has decreased

dramatically in the last three decades mainly due to increased awareness of the complication and early intervention of angiotensin converting enzyme inhibitors (ACEI) (Steen and Medsger 2007).

Pulmonary manifestations of SSc include pleural effusions, aspiration pneumonia secondary to oesophageal dysmotility, interstitial lung disease (ILD) and pulmonary hypertension (PH). Systemic sclerosis-related ILD is one of the most common causes of death in SSc (Tyndall, Bannert et al. 2010). Pulmonary hypertension can be either secondary to ILD or occur as isolated pulmonary arterial hypertension. The latter is a major cause of death in patients with longstanding LcSSc. A UK study reported the prevalence of pulmonary hypertension standing at 12% (Mukerjee, St George et al. 2003).

The commonest cardiac complication in SSc is cor pulmonale and right heart failure secondary to pulmonary hypertension. Primary cardiac involvement is rare and can present as arrhythmias, pericardial disease or myocardial involvement (Plastiras and Toumanidis 2012).

1.6.2 Autoantibody profile

Systemic sclerosis is associated with several autoantibodies. It is unclear whether these antibodies directly contribute to disease process or are a result of the disease pathogenesis itself (Ho and Reveille 2003). Up to 90% of patients will have a positive antinuclear test. Several specific antinuclear antibodies have been described in SSc. The most common of these are the anti-topoisomerase 1 (ATA) (also known as anti-Scl-70), anticentromere and anti-RNA polymerase III (Anti-RNAP) antibodies (Salazar, Assassi et al. 2015).

Antitopoisomerase-1 antibodies target type 1 topoisomerase; an enzyme responsible for relaxing DNA strands within the nucleus. These antibodies are commonly seen in patients with DcSSc and ILD. They are also prevalent in some populations like the Japanese and less in Caucasians

(Walker and Fritzler 2007, Grassegger, Pohla-Gubo et al. 2008) . Anticentromere antibodies occur mostly in Caucasian patients with LcSSc and are rarely seen in Black Africans. (Pudifin, Dinnematin et al. 1991).

These autoantibodies have prognostic implications with the ATA and anti-RNAP carrying the worst prognosis and ACA, anti U1 RNP and anti PM Scl associated with a better prognosis.(Ho and Reveille 2003). The ATA, anti–fibrillarin (U3RNP) and anti-RNAP are found mostly in DcSSc, whereas ACA, anti-PM Scl, anti-U1RNP and anti –Th/To are found mainly in LcSSc (Ho and Reveille 2003).

1.6.3 Classification criteria

The first classification criteria for SSc were developed by the American College of Rheumatology (ACR). These criteria included skin thickening proximal to the metacarpophalangeal joints as the major criterion, and sclerodactyly, digital pitting scars, and bibasilar pulmonary fibrosis as the minor criteria. A patient with either the major criteria or 2 of 3 minor criteria was said to fulfil the criteria for SSc . These criteria were found to be insensitive to recognising early disease. In Leroy and Medsger‘s criteria for early diagnosis and classification of SSc, they proposed the inclusion of nailfold capillary changes and SSc-specific autoantibodies for the classification of SSC (LeRoy and Medsger 2001).

As recent as 2013, the ACR/EULAR classification criteria for SSc were published. These criteria include more clinical and serological features which are given different weightings. (van den Hoogen, Khanna et al. 2013). Patients with an overall score of 9 or more are deemed to have SSc. (see Appendix C)(van den Hoogen, Khanna et al. 2013) . These criteria allow for earlier diagnosis of the condition.

1.7 Natural history, morbidity and mortality

1.7.1 Natural history of SSc

The natural history of the disease shows that there are variations to the disease subset. Patients with DcSSc tend to have a more aggressive course with early organ involvement than LcSSc, which tends to have a relatively benign course with late onset of complications like pulmonary hypertension, as shown in Figure 1

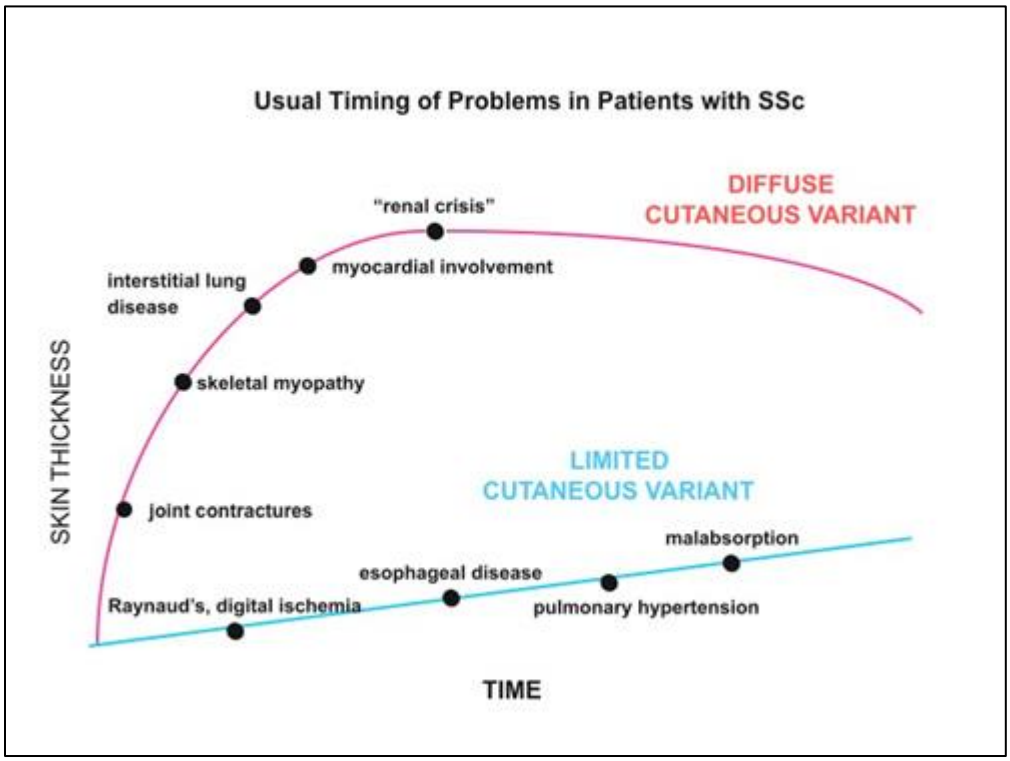


Figure 1: Natural history of SSc (Steen and Medsger 1990)

1.7.2 Trends of mortality in SSc

Studies from various countries show a wide variation in outcome (Kuwana, Kaburaki et al. 1994, Ruangjutipopan, Kasitanon et al. 2002, Hesselstrand, Scheja et al. 2003, Czirjak, Kumanovics et al. 2008). In one US centre, the 10-year cumulative survival has improved significantly from 53% in the 1970s to 67% in the 1990s (Steen and Medsger 2007).

SSc is associated with high mortality compared to the general population, and in a Swedish study, the standardised mortality rate for SSc was found to be 4.6 (Hesselstrand, Scheja et al. 1998). Survival rates have been reported to vary by geographical location and disease subset. In industrialised countries the average 5 and 10 year survival rates are at best 80% and 70% respectively. A 10 year survival rate of 92% in lcSSc versus 65% in dcSSc has been reported in a Canadian study (Al-Dhaher, Pope et al. 2010).

Table 2: Summary of survival rates in SSc

Location	Year	5 year/ 10 year survival (%)	% dcSSc
Sweden(Hesselstrand, Scheja et al. 1998)	1998	86/69	25
Spain(Joven, Almodovar et al. 2010)	2010	85/75	31
Taiwan(Kuo, See et al. 2011)	2011	83.2/-	-
Canada(Al-Dhaher, Pope et al. 2010)	2010	90/82	37
UK(Bryan, Howard et al. 1996)	1996	87/75	46
Hungary(Czirjak, Kumanovics et al. 2008)	2007	84/72.6	27.6
Iran(Poormoghim, Andalib et al. 2016)	2016	92.9/82.3	40

There has been a great shift in mortality rates in recent times. Studies have shown substantially improved outcomes that can be attributed to early and improved screening of organ involvement. The effective management of scleroderma renal crisis with the use of ACEI has resulted in a substantial reduction in mortality. Despite this, SSc is still associated with a high mortality as shown by the fact that more than half of deaths are directly related to the disease itself (Tyndall,

Bannert et al. 2010) (Al-Dhaher, Pope et al. 2010). Survival is significantly low among women with diffuse disease with or without organ complication (Laing, Gillespie et al. 1997), and survival outcome is also worse in Black patients than Caucasian (Laing, Gillespie et al. 1997).

1.7.3 Causes of death in SSc

Causes of death in SSc are generally categorised in to two; those that are directly disease-related or disease-unrelated. Disease related causes of death are those that are caused by SSc organ involvement, for example pulmonary fibrosis. Deaths due to disease-unrelated causes include infections and malignancies. Most deaths are disease-related, with ILD being the most common in dcSSc, and PAH in lcSSc (Barnes and Mayes 2012). Moreover, the spectrum of causes of death has changed over the last two to three decades in industrialised countries as depicted in Figure 2 (Steen and Medsger 2007). This US study showed a significant decline in deaths due to SRC over the last 3 decades. Today, pulmonary fibrosis (ILD) and pulmonary hypertension rank as the top causes of death.

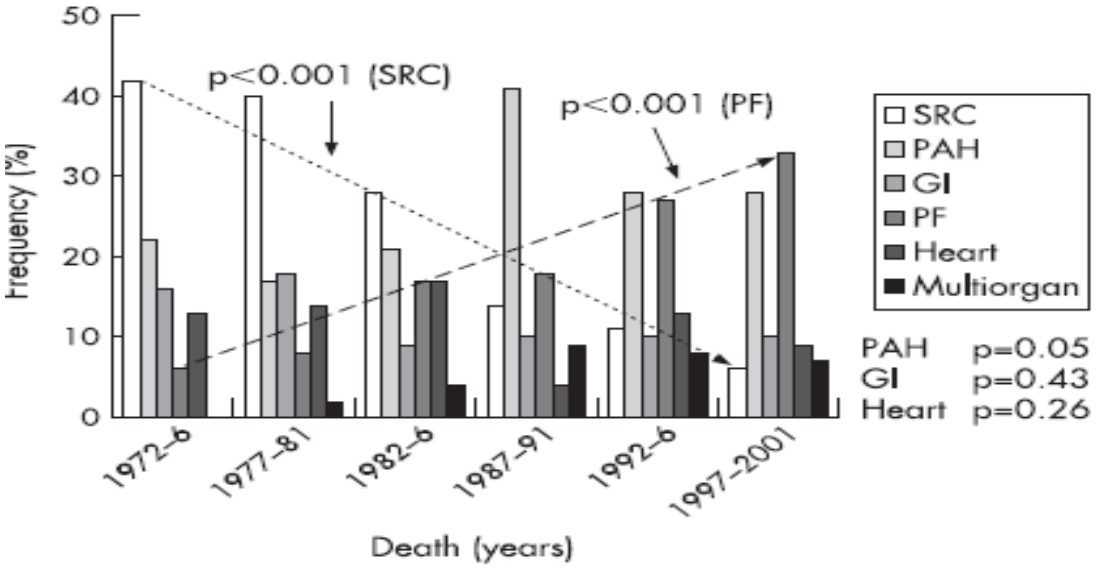


Figure **2: Changes in the causes of death (Steen and Medsger 2007)**

1.7.4 Predictors of mortality in SSc

Multiple studies have reported on the predictors of survival in SSc. Risk factors that have been identified as poor prognostic factors include dcSSc, proteinuria, PAH, FVC<80% of the normal, presence of dyspnoea, younger age at onset of RP, low diffusion capacity of the lung for carbon monoxide (DLCO) and high modified Rodnan skin score (mRSS). Other predictors of mortality that have previously been described include, male gender, an elevated erythrocyte sedimentation rate (ESR), earlier age at diagnosis and black ethnicity (Al-Dhaher, Pope et al. 2010). In all these predictors, men have a worse prognosis than women (Joven, Almodovar et al. 2010).

1.8 Principles of management

There is currently no single cure for SSc. The approach to management is individualised and based on the extent of organ involvement. Management of vascular complications is aimed at improving peripheral circulation and reducing PAH. Thus, treatment options include calcium channel blockers, prostaglandin analogues, phosphodiesterase 5 inhibitors, and endothelin receptor antagonists, alpha-blockers, serotonin inhibitors and angiotensin II receptor inhibitors.

The mainstay of therapy for the fibrotic complications such as ILD is immunosuppression drugs including cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab. Autologous haemopoietic stem cell transplantation has been used to treat severe refractory cases in some centres. As indicated above ACEI are effective in the management of SSc (Matucci-Cerinic, Steen et al. 2007)

Treatment of GIT complications is mainly symptom based, with use of proton pump inhibitors (PPI) for reflux oesophagitis , cauterization or laser probe therapy for gastric antral vascular ectasia (GAVE), antibiotic therapy for bacterial overgrowth and the use of high fibre diets and laxatives for patients with constipation (Tian and Zhang 2013).

Table 3: Summary of therapeutic options (Balbir-Gurman and Braun-Moscovici 2012)

Clinical feature	Treatment options
Raynaud's phenomenon	Calcium channel blockers, alpha-blockers, serotonin inhibitors, angiotensin II receptor inhibitors, local nitrates, iloprost
Digital ulcers healing	Iloprost, phosphodiestherase inhibitors
New digital ulcers prevention	Bosentan
Scleroderma	Methotrexate
Alveolitis	Cyclophosphamide (with/without corticosteroids), azathioprine
Pulmonary arterial hypertension	Endothelin receptors antagonists, phosphodiestherase inhibitors, prostanoids
Esophageal reflux	Proton pump inhibitors, pro-kinetics
Intestinal bacterial overgrowth	Broad spectrum antibiotics
Arthritis	Corticosteroids, methotrexate
Myositis	Corticosteroids, methotrexate, immunoglobulins
Serositis (pericarditis, pleuritis)	Corticosteroids, cyclophosphamide
Scleroderma renal crisis	Angiotensin converting enzymes inhibitors, angiotensin II receptors inhibitors

1.9 Aims and objectives of the present study

The aim of this study was to investigate the spectrum of causes of death in patients with SSc at Chris Hani Baragwanath Academic Hospital. The primary objectives were to determine disease-related and disease unrelated causes of death in SSc. The secondary objectives were to identify demographic, clinical and laboratory predictors of death and to estimate the 5 year and 10 year survival rates of SSc patients.

CHAPTER TWO: PATIENTS AND METHODS

2.1 Study design

A retrospective record review study of clinical records of SSc patients attending the Connective Tissue Disease Clinic at Chris Hani Baragwanath Academic Hospital, a tertiary level hospital in Soweto (South Western Township) in Gauteng was carried out. This hospital occupies 0.7km² (170 acres), with approximately 3200 beds and around 6760 staff members. The facilities are housed in 429 buildings with a total surface area of 233759 m². It is the third largest hospital in the world serving the community of Soweto, a region in the south of Johannesburg with a population of about 1.2 Million.

Inclusion criteria were patients older than 18 years of age at first diagnosis, fulfilling the ACR/EULAR classification criteria for SSc(van den Hoogen, Khanna et al. 2013) , adequate clinical records with at least 2 clinic visits, 6 months apart and seen at the Connective Tissue Clinic from 1 Jan 1990 to 31 December 2015. Patients who were deemed to have overlap connective tissue syndrome and those with inadequate clinical records were excluded from the study. .

2.2 Data variables

Data variables that were abstracted from clinical records using a prepared data collection sheet (see Appendix 1) included demographics such as age, sex, and ethnicity and smoker status, disease subset as defined by the Leroy and Medsger criteria (LeRoy, Black et al. 1988), and clinical features. The latter included: skin, musculoskeletal, cardiac, respiratory, gastrointestinal and renal manifestations of the disease. Laboratory investigations that were captured included: haemoglobin (Hb), (ESR), C reactive protein (CRP), complement (C3, C4), creatine kinase (CK)

and autoantibodies. The definitions for the clinical data and laboratory data are shown in Appendix A.

Deaths were confirmed from clinical records and the hospital registry. The causes of death were based on available clinical records and were further divided into those deemed to be directly, indirectly or unrelated to SSc. Outcomes were defined as known dead, known alive or lost to follow up on 31 December 2015. Survival times were calculated from date of diagnosis to death.

Data was anonymized by allocating each patient a study number so that no personal details of individual patients were known. The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Clearance Certificate: Appendix D) and conducted in line with the Declaration of Helsinki principles.

2.3 Statistical methods

Data were captured on Microsoft excel spreadsheet. It was then imported to a statistical package (STATA and Statistica). Univariate statistical analysis was performed applying either the one-way ANOVA test in the case of continuous variables and chi-square test (with Yates' correction) or Fisher's exact test for categorical variables. Survival curves were constructed using the Kaplan–Meier method. Univariate Cox proportional hazard regression model was applied to determine predictors of death. A p-value <0.05 was considered statistically significant.

CHAPTER THREE: RESULTS

3.1 Overview of data analysed

As shown in Figure 2, of the 291 case records reviewed of patients seen at the Connective Tissue Disease clinic during the period 1990 to 2015, 282 fulfilled the criteria for SSc. Thirty patients were excluded due to presence of overlap syndrome. A further number of 78 patients were excluded due to inadequate data and a follow up duration of less than 6 months. Thus, only 174 records were included in the final analysis.

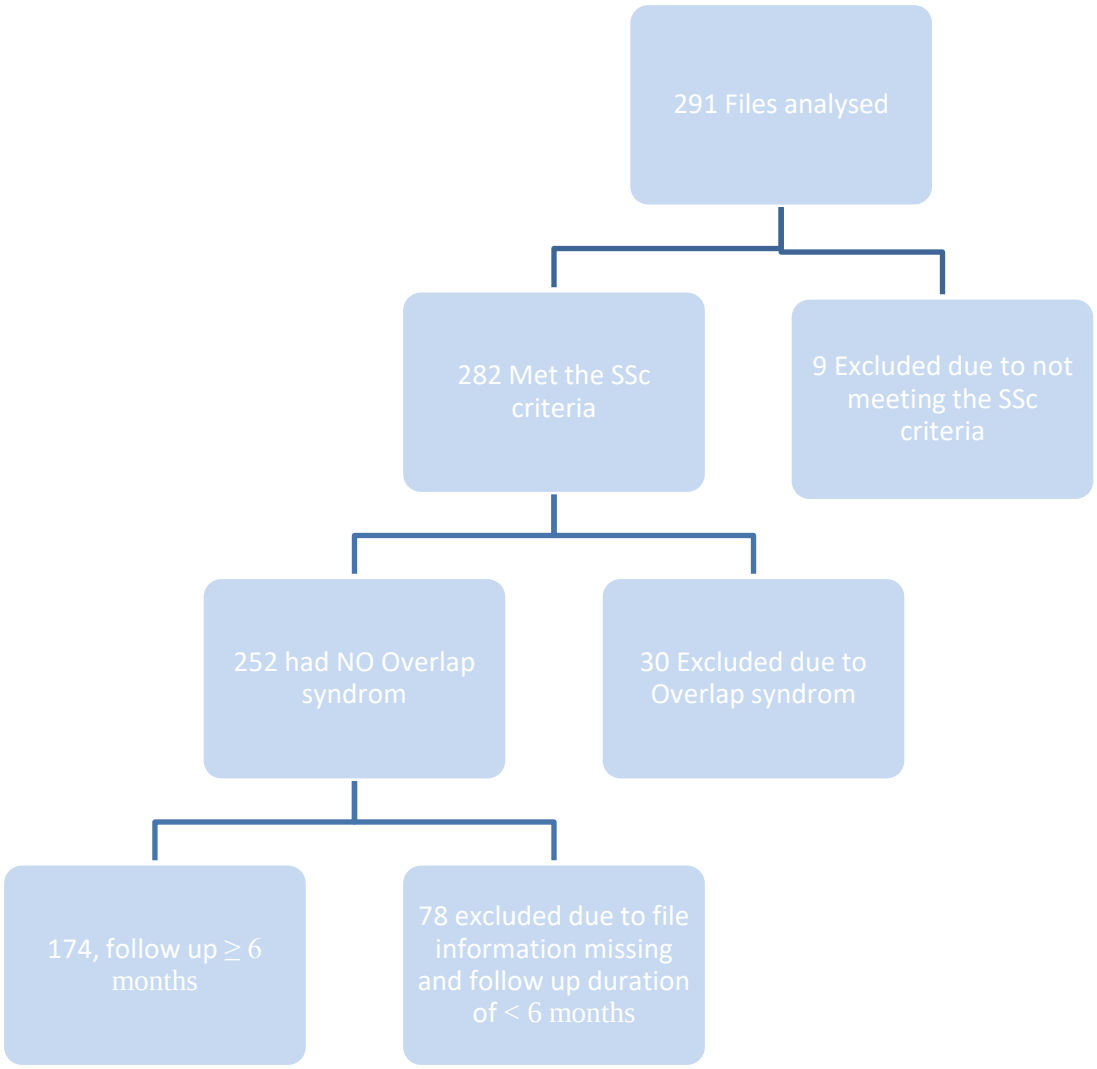


Figure 3: Summary of records reviewed

3.2 Demographics

Table 4 shows the demographics of the 174 patients. The majority of the patients were females comprising 87.4 % of the cases. The female to male ratio was 7:1. Regarding ethnicity, a large proportion (92.5%) of the patients were Black versus 6.9 % belonging to other ethnic groups. The mean age at diagnosis was 42 years with a range of 13 years to 73 years. The mean follow up duration was 65.8 months. A total number of 128 (73.6%) were classified as DcSSc and 44 (26.4%) as LcSSc. The number of patients lost to follow up was 63 (36.2%) and the number of known deaths was 58, constituting 33.3 % of cases recorded.

Table 4: Demographical features and outcomes of patients

	DcSSc(n=128)	LcSSc(n=46)	All SSc (n=174)
Gender (F)	108 (71.1%)	44 (96%)	152 (87.4%)
F:M	5:1	22:1	7:1
Ethnic group			
Black	121 (94.5%)	40 (87.0%)	161(92.5%)
Asian	2 (1.6%)	2 (4.4%)	4(2.3%)
White	2 (1.6%)	2 (4.4%)	4(2.3%)
Coloured	3 (2.3%)	1 (2.1%)	4(2.3%)
Unknown	0 (0%)	1 (2.1%)	1(0.6)
Alive	35 (27.3%)	18 (39.1%)	53 (30.5%)
Dead	49 (38.3%)	9 (19.6%)	58(33.3%)
Lost to follow up	44 (34.4%)	19 (41.3%)	63(36.2%)
Mean age at diagnosis in years (S.D)	41.8 (13.0)	42.5 (13.2)	42 (13.1)
Mean follow up duration in months (S.D)	67.1 (66.4)	62.1 (66.6)	65.8 (66.4)

(F-female, M-male, DcSSc-diffuse cutaneous systemic sclerosis, LcSSc-limited cutaneous systemic sclerosis, SSc-systemic sclerosis)

3.3 Clinical and laboratory features

Table 5 shows the frequency of clinical features at presentation and cumulative frequency. The most common clinical findings at onset for SSc were RP in 89.1% followed by arthralgias (64.4%) and digital ulcers (59.8%). With regards to the cumulative frequency, RP was the commonest feature (93.1%) followed by digital ulcers (71.3%) and arthralgia (74.1%). More than half of the patients had ILD (53.5%), while 35.1% had pulmonary hypertension.

Table 5: Summary of clinical features of patients at onset and cumulatively

	Clinical features	
	At onset n=174 (%)	Cumulative n=174 (%)
Raynaud's phenomenon	155 (89.1%)	162 (93.1%)
Digital ulcers	104 (59.8%)	124 (71.3%)
Digital gangrene	4 (2.3%)	15 (8.6%)
Telangiectasia	26 (14.9%)	55 (31.6%)
Calcinosis	17 (9.8%)	41 (23.6%)
Arthritis	42 (24.1%)	54 (31.0%)
Arthralgia	112 (64.4%)	129 (74.1%)
Joint contractures	25 (14.4%)	53 (30.5%)
Myopathy	52 (29.9%)	66 (37.9%)
Myositis	27 (15.5%)	35 (20.1%)
Tendon friction rubs	8 (4.6%)	15 (8.6%)
Interstitial lung disease	56 (32.2%)	93 (53.5%)
Pulmonary hypertension	19 (10.9%)	61 (35.1%)
Cor pulmonale	6 (3.4%)	30 (17.2%)
Pleural effusion	2 (1.1%)	8 (4.6%)
Pericardial effusion	9 (5.2%)	18 (10.3%)
Serositis	11 (6.3%)	26 (14.9%)
Pericarditis	1 (0.6%)	5 (2.9%)
Hypertension	40 (23.0%)	66 (37.9%)
Upper gastrointestinal symptoms	112 (64.4%)	147 (84.5%)
Lower gastrointestinal symptoms	4 (2.3%)	18 (10.3%)
Proteinuria	8 (4.6%)	42 (24.1%)
Renal dysfunction	7 (4.0%)	27 (15.5%)
Scleroderma renal crisis	2 (1.1%)	5 (2.9%)

Table 6 shows the frequency of laboratory features at onset and cumulative frequencies. Anaemia was observed in 22.4% at onset and 54.0% overall. The ANA was positive in 85.1 % of patients, in whom the cumulative ACA positivity was 8.0%, and 20.7 % of patients for ATA. The cumulative frequencies of antibodies to RNP, Sm, Ro and La were 29.9%, 12.6%, 24.7% and 10.3% respectively. A high CRP was found in 58.6% and high ESR in 77.6% of patients.

Table 6: Summary of serological features of patients at onset and cumulative

Serological Features		
	Onset	Cumulative
Anaemia(F<11,M<13)	39 (22.4%)	94 (54.0%)
High ESR(>28)	74 (42.5%)	135 (77.6%)
High CRP(>10)	47 (27.0%)	102 (58.6%)
Low C3	4 (2.3%)	9 (5.2%)
Low C4	13 (7.5%)	35 (20.1%)
CK>140	51 (29.3%)	97 (55.7%)
ANA	148 (85.1%)	148 (85.1%)
ACA +	13 (7.5%)	14 (8.0%)
AntiDsDna	2 (1.1%)	3 (1.7%)
Anti-RNP	39 (22.4%)	52 (29.9%)
Anti-Sm	18 (10.3%)	22 (12.6%)
Anti-Ro	31 (17.8%)	43 (24.7%)
Anti-La	12 (6.9%)	18 (10.3%)
ATA	32 (18.4%)	36 (20.7%)
Jo antibodies	1 (0.6%)	3 (1.7%)

F-female, M-male, ESR-erythrocyte sedimentation rate, CRP-C reactive protein, C3-complement 3, C4-complement 4, CK-creatine kinase, ANA-antinuclear antibodies, ACA-anticentromere antibodies, DsDNA-double stranded deoxyribose nucleic acid, RNP-antiribonucleoprotein antibodies, Sm- anti-Smith antibodies, Ro-antibodies to Ro protein, La-antibodies to La protein, ATA- antibodies to topoisomerase 1, Jo antibodies-antibodies to antibody directed against the antihistidyl–tRNA synthetase.

Table 7: HIV and TB frequencies

	Onset	Cumulative
HIV	7 (4.0%)	12 (6.9%)
Pulmonary TB	2 (1.2%)	9 (5.2%)
Extrapulmonary TB	0 (0%)	2 (1.1%)
Overall TB	2 (1.2%)	11(6.3%)

HIV-human immunodeficiency virus, TB-tuberculosis

As shown in Table 7, the frequency of HIV in our cohort was 6.9%. The overall frequency of tuberculosis (TB) was 6.3%

Drug therapy

The most commonly used drugs were proton pump inhibitors (PPI) (71.8%), calcium channel blockers (CCB) (57.5%), ACEI (47.1%), steroids (46.0%) and cyclophosphamide (24.7%) (Table 8)

Table 8: Summary of drug therapy

	All n=174(%)
Corticosteroids	80 (46.0%)
Cyclophosphamide	43 (24.7%)
Azathioprine	26 (14.9%)
Methotrexate	31 (17.8%)
Mycophenolate mofetil	6 (3.4%)
Iloprost	17 (9.8%)
Omeprazole(PPI)	125 (71.8%)
Angiotensin converting enzyme inhibitorsACEI	82 (47.1%)
Calcium channel blockers	100 (57.5%)
D-Penicillamine	30 (17.2%)
Statin	23 (13.2%)
Aspirin	22 (12.6%)

PPI-proton pump inhibitors, ACEI-angiotensin converting enzyme inhibitors

3.4 Causes of death in SSc patients

There were 58 known deaths recorded, representing a third of the total cohort. The causes of death are shown in Table 9 below. Of the known causes of death, 20 (34.5%) were deemed to be disease-related, and 8 (13.8%) to be disease-unrelated. Of the disease related deaths, majority was ILD/Cor pulmonale, 2 were from vascular complications, and 4 were from cardiac complications and only 1 patient died from SRC. Of the disease unrelated deaths, most were due to infections accounting for more than half of the deaths not related to SSc. In 30 cases, the cause of death was unknown but verified by hospital registrar and home affairs.

Table 9: Causes of known deaths in 58 patients

	All SSc N=58	DcSSc N=49	LcSSc N=9
Total Deaths	58/174 (33.3%)	49/128 (38.2%)	9/46 (19.6%)
Known cause of death	28/174 (16.0%)	24/128 (18.9%)	4/46 (8.7%)
Disease related	20 (71.4%)	17 (70.8%)	3(75.0%)
• **ILD/Cor Pulmonale**	13	11	2
Isolated PAH	1	0	1
PH with ILD	11	11	0
ILD no PHT	1	0	1
• **Vascular involvement**	2	1	1
• **Cardiac involvement**	4	4	0
• **Renal involvement**	1	1	0
Disease unrelated	8(28.6%)	7(29.2%)	1(25.0%)
• **Malignancy**	2	1	1
• **Infections**	5	5	0
• **Others**	1	1	0
Unknown	30 (51.7%)	25(51.0%)	5(55.5%)

SSc-systemic sclerosis, DcSSc-diffuse cutaneous systemic sclerosis, LcSSc-limited cutaneous systemic sclerosis, ILD- interstitial lung disease, PAH-pulmonary arterial hypertension, PH-pulmonary hypertension

3.5 Kaplan Meier survival analysis

The median overall survival rate of patients with SSc censored for those lost to follow up was at 56.3 % and 35.8 % at 5 years and 10years respectively. As shown in Table 10, univariate cox regression analysis showed significant differences in worse survival rates for patients with high CRP, upper GIT symptoms, cor pulmonale/pulmonary hypertension, renal dysfunction and proteinuria. The survival outcome was worse in DcSSc compared to LcSSc. However, this did not reach statistical difference with a p-value of 0.14 (Figure 4). Statistical significance in outcomes was seen in patients with digital ulcers compared to those who did not have digital ulcer with p-value 0.0368 (Figure 5). The former were were also associated with a worse survival outcome. There was difference in survival outcome between patients with ILD compared to without ILD (Figure 10). The presence of telangiectasia was assoicated with a better outcome.

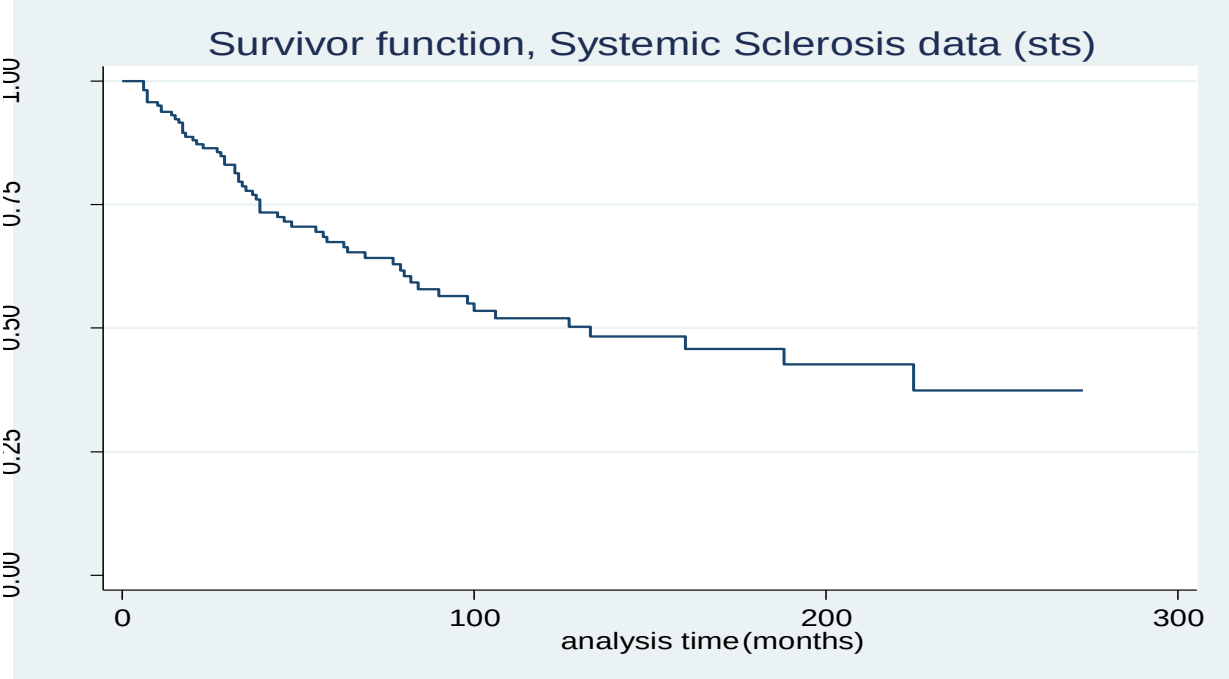


Figure 4: Overall survival in SSc

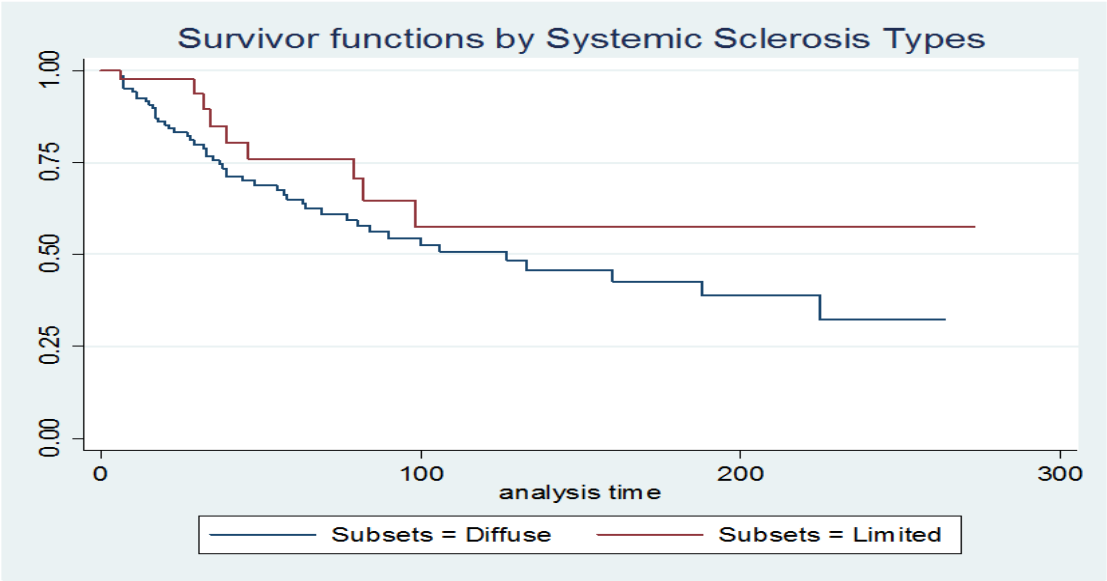


Figure 5: Overall survival by disease subtype (p=0.14)

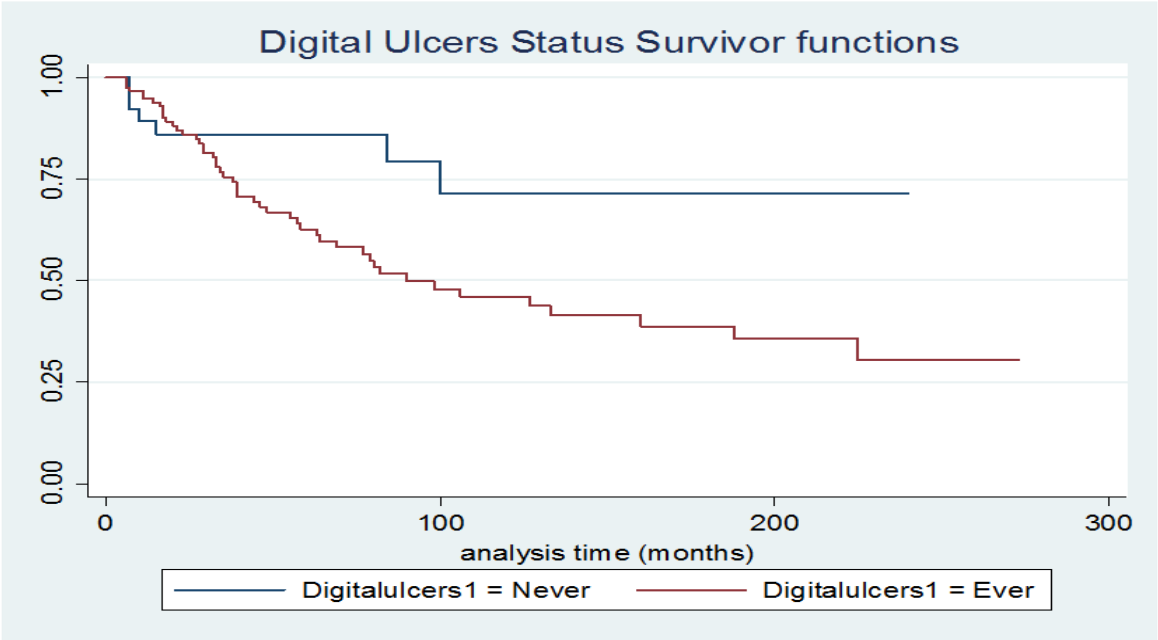


Figure 6: Overall survival with or without digital ulcers (P=0.04)

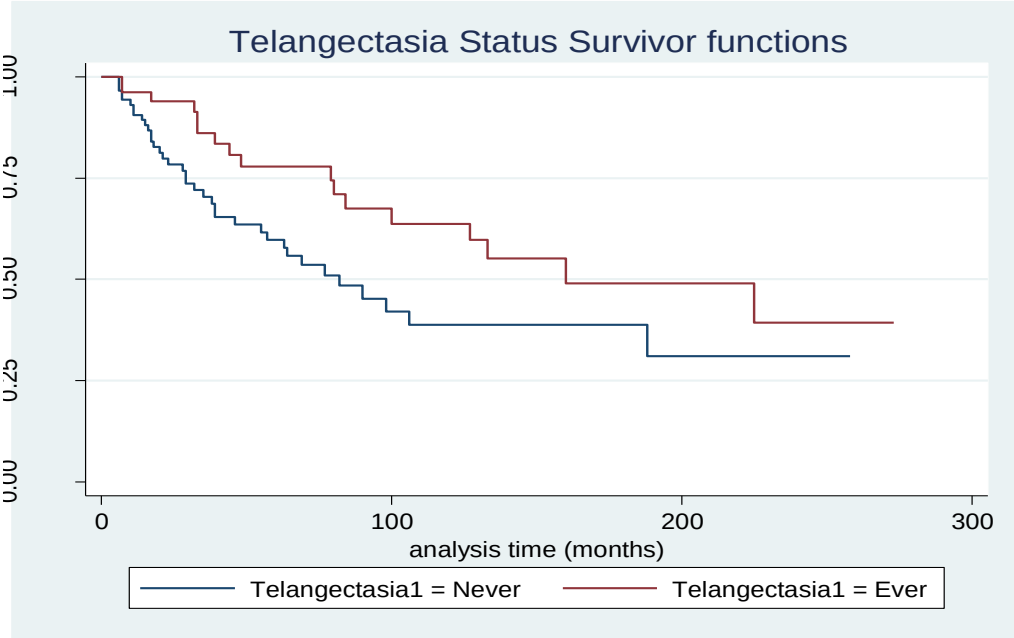


Figure 7: Overall survival with and without telangiectasia (P=0.04)

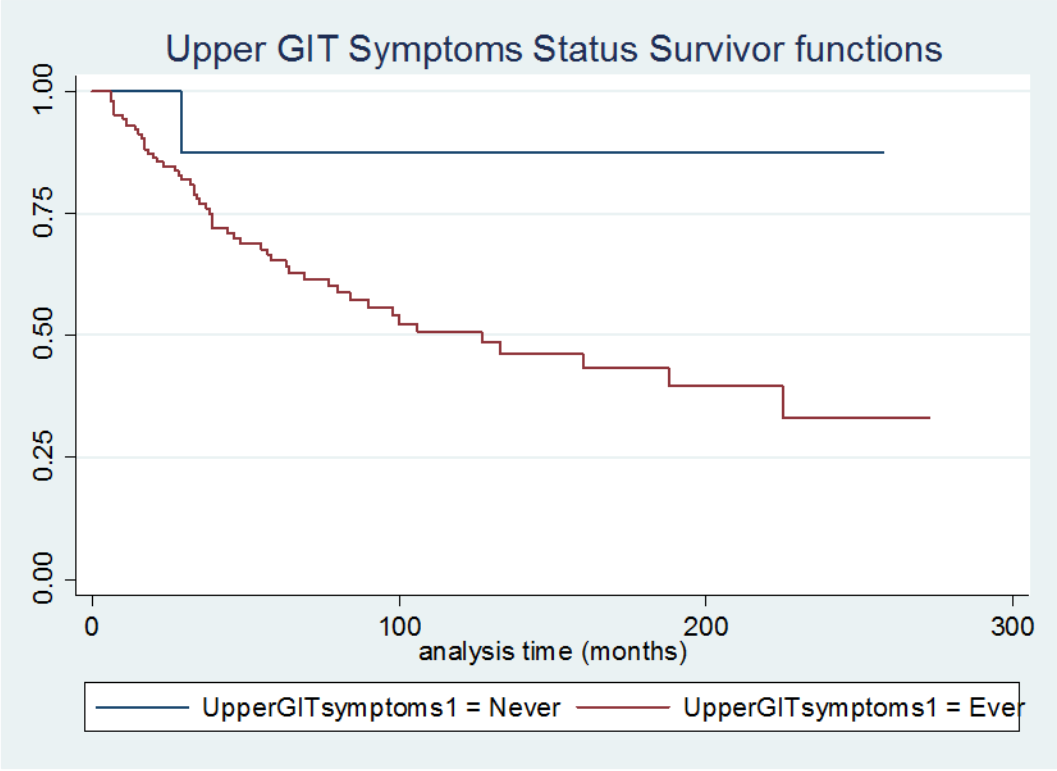


Figure 8: Overall survival with or without upper GIT symptoms (P=0.04)

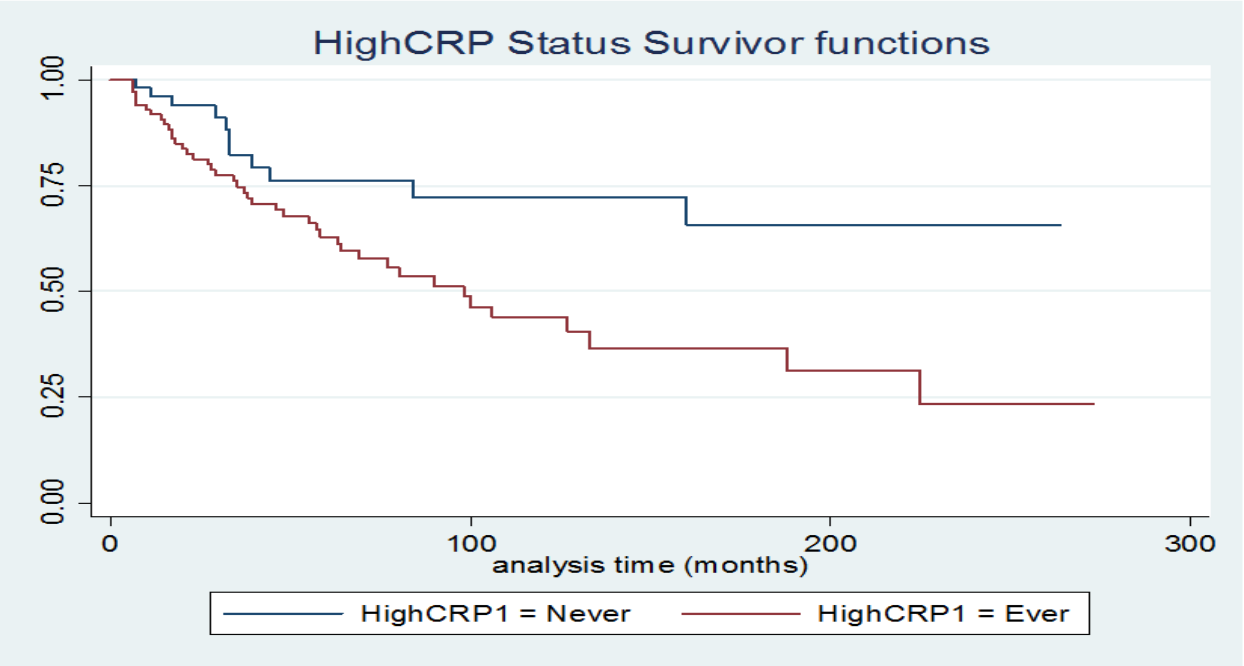


Figure 9: Overall survival with or without high CRP (P=0.01)

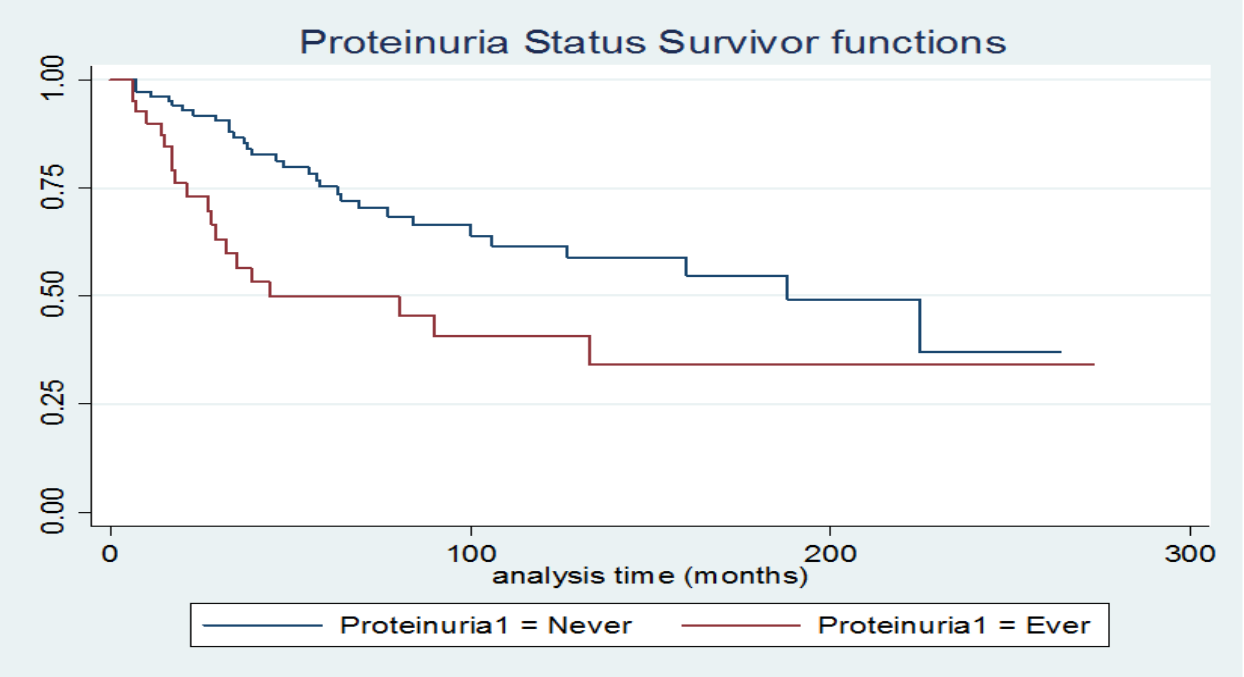


Figure 10: Overall survival of with or without proteinuria (P=0.01)

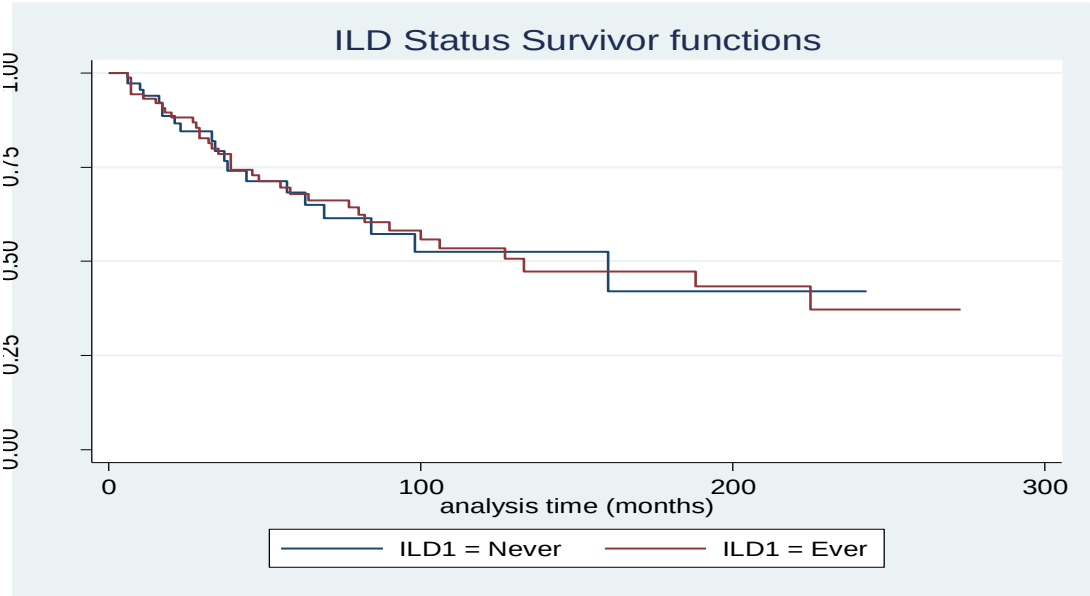


Figure 11: Overall survival with or without interstitial lung disease (P=0.96)

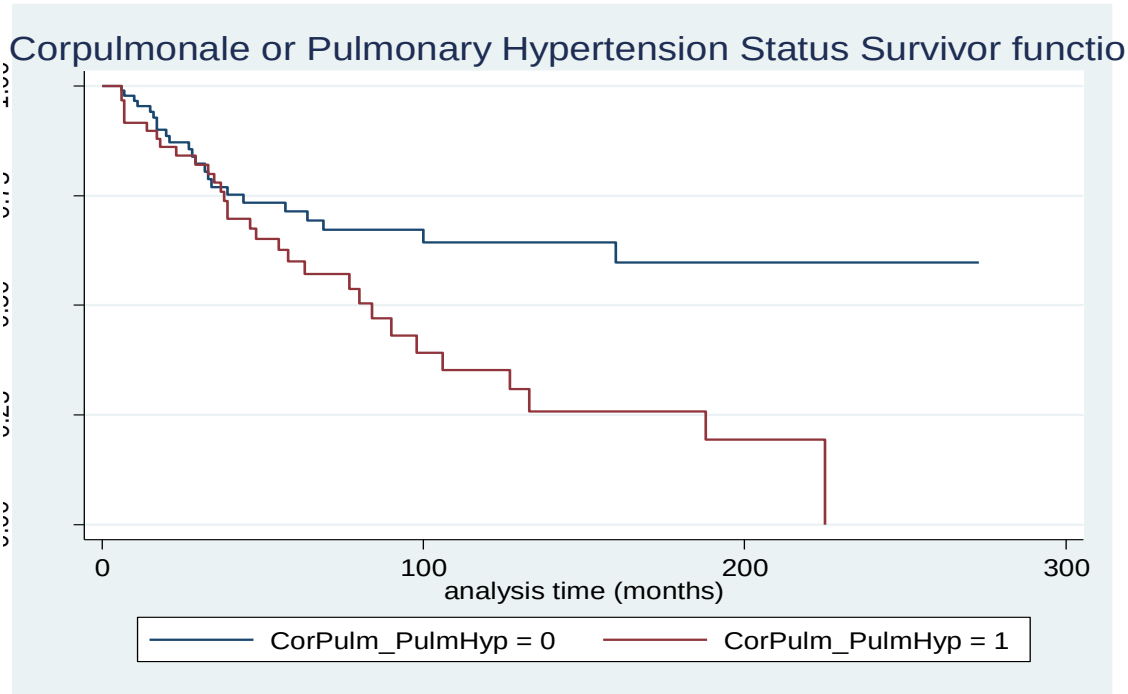


Figure 12: Overall survival with or without cor pulmonale / pulmonary hypertension (p=0.01)

3.6 Predictors of mortality in SSc patients

Univariate cox analysis was performed, this is shown in Table 10. This demonstrated a high hazard ratio of statistical significance in patients with digital ulcer (HR 2.27), Telangiectasia (HR0.54), Cor pulmonale, pulmonary hypertension (HR 2.10), Serositis (HR30.6), proteinuria (HR2.08), renal dysfunction (HR2.99) and a high CRP (HR 2.47).

Table 10: Summary of Univariate Cox regression modelling for prognostic factors for mortality in SSc

	Hazard. Ratio	p-value	[95% Conf. Interval]	
Gender	1.24	0.601	0.56	2.73
Race	0.59	0.378	0.18	1.90
Age of onset of symptoms	1.01	0.429	0.99	1.03
Smoker	0.86	0.572	0.52	1.44
Raynaud's phenomenon	1.13	0.864	0.28	4.65
Digital ulcers	2.27	0.043	1.03	5.02
Digital gangrene	1.10	0.809	0.50	2.44
Telangiectasia	0.54	0.038	0.30	0.97
Calcinosis	1.06	0.850	0.59	1.89
Arthritis	0.83	0.499	0.48	1.43
Joint contractures	0.98	0.938	0.57	1.68
Myositis	0.79	0.478	0.41	1.51
Tendon friction rubs	1.02	0.971	0.40	2.60
Interstitial lung disease	0.99	0.960	0.57	1.71
Cor Pulmonale/Pulmonary Hypertension	2.10	0.008	1.22	3.63
Serositis (pericardial and pleural effusion)	30.59	0.000	5.93	157.68
Hypertension	0.68	0.175	0.40	1.18
Upper GIT symptoms	6.03	0.075	0.83	43.68
Proteinuria	2.08	0.011	1.18	3.66
Renal dysfunction	2.99	0.000	1.65	5.40
SRC	3.23	0.053	0.98	10.62
Anaemia	0.99	0.967	0.57	1.70
High ESR	1.04	0.921	0.45	2.45
High CRP>10	2.47	0.008	1.27	4.80
LowC3 andC4	0.99	0.982	0.53	1.87
Sm	0.96	0.920	0.43	2.14
Ro	0.72	0.337	0.37	1.40
La	1.13	0.772	0.50	2.52
HIV	2.14	0.120	0.82	5.60

GIT-gastrointestinal tract, SRC-scleroderma renal crisis, ESR-erythrocyte sedimentation rate, CRP- C reactive protein, C3- complement 3, C4-complement 4, Sm- antibodies against Smith

protein, Ro- antibodies against Ro protein , La- antibodies against La protein , HIV- human immunodeficiency virus

CHAPTER FOUR: DISCUSSION AND CONCLUSIONS

This record review represents one of the only studies on deaths and causes thereof in SSc in Sub-Saharan Africa.

4.1 Demographics

In this study of predominantly black South Africans, the subset distribution was predominantly DcSSc (73.6%), which differs from that reported in Caucasians where the predominant subset was LcSSc. (Hesselstrand, Scheja et al. 1998, Strickland, Pauling et al. 2013). These racial differences are consistent with findings in US studies where DcSSc was seen more in women of African American descent compared to Caucasian women (Laing, Gillespie et al. 1997).

The female to male ratio of 6.9:1 is higher than the (ratio) reported in a recent Egyptian study.(Moneima, Darweesha et al. 2013), but similar to that reported in the UK of 7:1 (Strickland, Pauling et al. 2013). The mean age at diagnosis of 42 years; is a younger age than that reported in UK, Spain, Taiwan and Denmark (Jacobsen, Halberg et al. 1998, Joven, Almodovar et al. 2010, Kuo, See et al. 2011, Strickland, Pauling et al. 2013).

4.2 Clinical features

The most common clinical feature was Raynaud's phenomenon, found in 93.1% of patients, and is similar to that reported in other studies(Meier, Frommer et al. 2012). Digital ulcers were observed in 59.8% at onset, which is numerically higher than the 36% observed in the EUSTAR cohort of predominantly Caucasian patients (Meier, Frommer et al. 2012). The cumulative

frequency of ILD (53.5%) is similar to that reported previously in a local study (56%) (Tager and Tikly 1999), and in African American with SSc (54%) (Steen, Domsic et al. 2012).

4.3 Serological features

All except 14.9 % of patients tested positive for the ANA. Antinuclear antibody negative SSc is a well-known and described phenomenon with a reported frequency of 5-16% (Steen 2005). Anticentromere antibody) was positive in only 8% of our patients, in agreement with 7.5% observed by Ashmore from the same institution(Ashmore, Tikly et al. 2018), and lower than that reported in Caucasians. This in part, is a reflection of the relative smaller proportion of patients in the present study having LcSSc, which is commonly associated with AC (Walker, Tyndall et al. 2007). Antitopoisomerase antibody was found in about a fifth of patients and is usually associated with diffuse disease and a poorer prognosis (Grassegger, Pohla-Gubo et al. 2008). The high percentage of patients with antiRNP antibodies is comparable to that reported in a previous study done in the United States of America (Nietert, Mitchell et al. 2006)

4.4 Deaths

The majority of the known causes of death in the present study were disease-related, and cardiopulmonary complications were the leading cause of death, similar to findings in other populations. (Tyndall, Bannert et al. 2010, Rubio-Rivas, Royo et al. 2014). Cardiopulmonary complications are known to carry a higher risk of death compared to other systemic manifestations (Komocsi, Vorobcsuk et al. 2012). Noteworthy is that only one patient in our study died due to SRC. This is in part due to the early use of ACEI in patients with SRC, which has been shown to reduce SRC related deaths significantly over the past 3 decades (Steen and Medsger 2007). In spite of our best efforts to determine the causes of death in all patients by examining mortuary records and Department of Home Affairs records, we were unable to determine the cause of the death in about half of the patients. We suspect that one of the reasons

for this was that most of these patients died at home, and the specific cause of death was not recorded by the attending health care professional.

4.5 Survival

As observed in several studies previously, DcSSc carried a worse prognosis than LcSSc. Of interest is that there was no difference in survival in patients with ILD compared to patients without ILD. This is similar to that seen in a South African study that focused specifically on ILD in SSc (Ashmore 2014).

4.6 Predictors for mortality

Several clinical features were associated with death. The risk for death was increased in patients with digital ulcers, Cor pulmonale, pulmonary hypertension, serositis, proteinuria, renal dysfunction and a high CRP. Serositis followed by renal dysfuction and digital ulcers conferred the highest risk for death. Although only a minority of patients have serositis in SSc, like our findings, this has also been found in a Spanish study (Joven, Almodovar et al. 2010). Similarly, renal dysfunction has also been reported as a predictor of death in Hungarian patients (Czirjak, Kumanovics et al. 2008). Surprisingly, telangiectasia was found to be protective. Telangiectasiae are a feature of long standing disease (Varga

2013), and are associated with pulmonary arterial hypertension and thus seen as a surrogate marker for small vessel disease (Shah, Wigley et al. 2010).

4.7 Limitations of the study

There are several limitations to the study. Inherent to most retrospective studies is the problem of missing data. Moreover, a large number of patients were lost to follow up making it difficult and almost impossible to ascertain whether they were alive or dead. Furthermore as indicated earlier in more than half the cases we were unable to ascertain the cause of death as these deaths occurred outside of the hospital.

4.8 Conclusion

In this retrospective review of mainly black South Africans with DcSSc, the majority of known deaths were disease-related and in particular due to ILD and Cor pulmonale. Predictors of death included serositis, proteinuria, renal dysfunction and a high CRP. Earlier and more effective medical interventions for cardiopulmonary complications are likely to reduce mortality in this disease that carries a dismal prognosis.

Disclosure statement

No conflict of interest

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APPENDIX A: SCLERODERMA RESEARCH DATA SHEET

Study number:
Age:

Sex :	M	F			Age of onset of symptoms : _____
Ethnic origin :	B	W	A	C	Date or Age of Diagnosis : _____
Smoker :	Y	N			

Alive on 31/12/2015 :	Y	N

Outcome :
Dead Alive Unknown Lost to follow up

Follow-up duration in months till 31/12/2015:

Subsets	Limited	Diffuse	Overlap
Skin			
Raynaud's phenomenon	0	1	2
Digital Ulcers	0	1	2
Digital gangrene	0	1	2
Telangiectasia	0	1	2
Calcinosis	0	1	2

Modified Rodnan Score
Score at diagnosis:
Highest Score:

Musculoskeletal			
Arthritis	0	1	2
Arthralgia	0	1	2
Joint contractures	0	1	2
Myopathy	0	1	2
Myositis	0	1	2
Tendon friction rubs	0	1	2

Cardio Respiratory

Interstitial lung disease

	At Diagnosis	Last Reading
Clinical		
x-ray changes		
DLCO		
FVC predicted %		
FEV1 / FVC		
HRCT		

Pulmonary hypertension	0	1	2
Cor pulmonale	Y	N	

Serositis

Pleural effusion	0	1	2
Pericarditis	0	1	2
Pericardial effusion	0	1	2
Hypertension	0	1	2

GIT `

Upper GIT symptoms	0	1	2
Lower GIT symptoms	0	1	2

Renal

Proteinuria	0	1	2
Renal dysfunction	0	1	2
Scleroderma renal crisis	0	1	2

Lab Results

Anaemia	0	1	2
High ESR	0	1	2
High CRP	0	1	2
Low C3	0	1	2
Low C4	0	1	2
High CK	0	1	2

ANA- highest titre + pattern			
dsDNA	0	1	2
RNP	0	1	2
Sm	0	1	2
Ro	0	1	2
La	0	1	2
ATA	0	1	2
Jo antibodies	0	1	2
HIV	0	1	2
Pulmonary TB	0	1	2
Extrapulmonary TB	0	1	2

Cause of death

Directly caused by scleroderma	
Indirectly caused by scleroderma	
Not caused by scleroderma	

SSc related death

Pulmonary

Interstitial lung disease	Y	N
Pulmonary arterial hypertension	Y	N
Others	Y	N

Cardiac

Arrhythmias	Y	N
Left heart failure	Y	N
Right heart failure	Y	N
Pericarditis	Y	N

Renal

Renal crisis	Y	N

Gastrointestinal	Y	N

Infections

Pneumonia	Y	N
Septicaemia	Y	N
Others	Y	N

Malignancy

Non-small cell lung cancer	Y	N
Small cell lung cancer	Y	N
Others	Y	N

Cardiovascular

Myocardial infarction	Y	N
Pulmonary Embolism	Y	N
Stroke	Y	N

Others	Y	N
Unknown	Y	N

Treatment	Route	Average dose	duration
Steroids			
Cyclophosphamide			
Methotrexate			
Azathioprine			
Mycophenolate mofetil			
Iloprost			

History of use of other drugs		
Calcium channel blockers	Y	N
ACEI/ARB	Y	N
Statin	Y	N
Aspirin	Y	N
Proton pump inhibitors	Y	N

Data sheet definitions

0- Not present
1- Present at diagnosis
2- Developed later in illness, after diagnosis

Skin

Raynaud's - Vasospasm resulting in pallor (white), cyanosis (blue) and/or hyperaemia (red)
Fingertip ulcers- ulcers distal to or at proximal interphalangeal joint not thought to be due to trauma
Fingertip pitting scars – depressed areas at digital tips as a result of ischaemia rather than trauma or exogenous causes
Digital gangrene
Modified Rodnan skin score
Score at onset
Highest score
Telangiectasia – Visible capillaries that blanch on pressure
Especially on the face and inside the mouth or skin
Calcinosis- Areas of calcium deposition

Musculoskeletal

Arthritis-documented synovitis
Arthralgia- painful joints
Joint contractures/deformities- Fixed flexion deformities or contractures due to tightening of skin
Myopathy- proximal muscle weakness.
Myositis- Peter Bowen's criteria clinical myopathy
Raised CK
EMG changes
Muscle biopsy proven

Cardiorespiratory

Interstitial lung disease - Clinical- Bibasal Velcro crackles
Chest X ray changes- basal interstitial/fibrotic changes
HRCT- honey combing, ground opacification, reticulonodular opacities, traction bronchiectasis
Lung functions- first and last reading if possible

Pulmonary hypertension- pulmonary artery pressures >40mmHg on echocardiogram
Specific ECG changes- right ventricular hypertrophy
And P pulmonale

Hypertension-BP>140/90 > 2 occasions

Serositis

Pleural effusion- Tapped and not infective
Pericarditis- Confirmed on echo/ ECG
Pericardial effusion- confirmed on echo

Renal

Proteinuria- 1+ protein or more on dipstick
Renal dysfunction- Urea>8mmol/L, Creatinine>100umol/L
Scleroderma renal crisis- Rapidly progressive renal failure, usually high BP, high creatinine, proteinuria and microscopic haematuria

GIT
Upper symptoms- heartburn, regurgitation, dysphagia, oesophagitis
Lower symptoms- diarrhoea, constipation, malabsorption, abdominal pain or distension

Lab results
All abnormal results present more than 50% of the time
Anaemia- male Hb <13g/dL/
Female Hb<11g/dL
High ESR>28
High CRP>10
Low C3 0,500- 1,530/ 0.90-1.80
Low C4 0,200- 1,000 /0.10-0.40
High CK> 140

All antibodies- 0, 1, 2
Drugs-0, 1, 2.

APPENDIX B: ACR 1980 CLASSIFICATION CRITERIA

Criterion	Definition
Major criterion	Proximal scleroderma
Or 2 or more of the following	
Minor criteria	Sclerodactyly Digital pitting scars of the fingertips or loss of substance of the distal finger pad Bilateral basilar pulmonary fibrosis

APPENDIX C: ACR/EULAR 2013 CLASSIFICATION CRITERIA

Item	Sub-item	Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers	Puffy fingers	2
	Sclerodactyly	4
Fingertip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nail fold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon		3
SSc related autoantibodies	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3

A score of equal or more than 9 is diagnostic of SSc

APPENDIX D: ETHICAL CLEARANCE CERTIFICATE

R14/49 Dr Zodwa Dire

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150327

NAME: (Principal Investigator)	Dr Zodwa Dire
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Causes and Predictions of Mortality in Systematic Sclerosis at a Tertiary Southern Gauteng Hospital
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M Tickly and Dr C Ickinger
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/04/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES