INTERSTITIAL LUNG DISEASE IN SOUTH AFRICANS WITH SYSTEMIC SCLEROSIS

Philippa Ashmore

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

Johannesburg, 2014

DECLARATION

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

Signed: _____

Date: _____ day of _____, 2014

Dedicated to my son

Drew Peter Ashmore

PRESENTATIONS ARISING FROM THIS STUDY

Poster presentation:

Ashmore P, Tikly M, Wong M, Ickinger C. *Interstitial Lung Disease in South Africans with Systemic Sclerosis*. 3rd Systemic Sclerosis World Congress, Rome 2014.

Oral presentation:

Ashmore P, Tikly M, Wong M, Ickinger C. *Frequency And Predictors Of Interstitial Lung Disease In Systemic Sclerosis.* University of the Witwatersrand Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. Johannesburg 2014.

ABSTRACT

BACKGROUND: Interstitial lung disease (ILD) is one of the leading causes of death in systemic sclerosis (SSc).

PATIENTS AND METHODS: A retrospective review of case records, over 20 years, of SSc patients attending a tertiary Connective Tissue Diseases Clinic. Comparisons between ILD and non-ILD groups at presentation were performed in order to identify baseline associations and predictors of ILD.

RESULTS: Of the 151 participants that met inclusion criteria, 60 (40%) had ILD. On multivariate analysis the only three variables to remain significant were median duration of disease (OR 1.2 (1.1-1.3); p<0.001), speckled anti-nuclear antibody (ANA) pattern (OR 2.95 (1.22-7.15); p=0.017) and bibasal crackles (OR 5.4 (2.1-13.5); p<0.0001).

Univariate analysis of baseline variables associated with interstitial lung disease in systemic sclerosis.

Baseline Variable	ILD (n=60)	Non-ILD (n=91)	OR (CI 95%)	*p*
Bibasal crackles (%)	28 *(46.7)*	10 *(11.0)*	7.1 (3.1-16.3)	<0.0001
Diffuse disease subtype (%)	49 *(81.7)*	45 *(48.9)*	4.6 (2.1-9.9)	<0.001
Limited disease subtype (%)	8 *(13.3)*	38 *(41.3)*	0.2 (0.1-0.5)	<0.001
Anti-centromere antibodies (%)	0 *(0.0)*	10 *(13.0)*	-	0.006
Cough (%)	21 *(35.0)*	15 *(16.5)*	2.7 (1.3-5.9)	0.007
Median duration in years *(IQR)*	6.1 *(8.3)*	4.0 *(5.0)*	2.2 (1.8-2.4)	0.009
Speckled ANA pattern (%)	29 *(50.9)*	25 *(32.5)*	2.5(1.2-4.9)	0.010
Dyspnoea (%)	27 *(45.0)*	24 *(26.4)*	2.3 (1.1-4.6)	0.014
Gold mining history (%)	5 *(8.3)*	1 *(1.1)*	8.2 (0.9-71.9)	0.037

ANA=antinuclear antibody; ILD=interstitial lung disease; IQR= interquartile range; OR=odds ratio

Additionally, dyspnoea was associated with ILD severity (p=0.008). Bibasal crackles (p=0.014), increased plasma urea (p=0.041), and reduced serum albumin (p=0.007) were associated with mortality in the ILD group.

CONCLUSION: Interstitial lung disease in South African SSc patients is common. The diffuse cutaneous disease subtype appears to drive the disease process. There should be a high index of suspicion for ILD in SSc patients presenting with a gold mining history, dyspnoea, cough and bibasal crackles.

ACKNOWLEDGEMENTS

I would like to acknowledge the invaluable contributions and guidance from my supervisors: Dr Claudia Ickinger and Professor Mohammed Tikly. Lucky Dube was exceptionally helpful in her role as filing clerk. Additionally, Manoj Chiba provided assistance with statistical analysis.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURE **PAGE**

LIST OF TABLES

TABLE **PAGE**

LIST OF ABBREVIATIONS

ACA	Anti-centromere antibody
AECA	Anti-endothelial cell antibodies
AFA	Anti-fibroblast antibodies
Alb	Albumin
ANA	Anti-nuclear antibody
ATA	Anti-topoisomerase I antibodies
BAL	Broncho-alveolar lavage
CHBAH	Chris Hani Baragwanath Academic Hospital
CI 95%	Confidence interval at 95% level of significance
Cr	Creatinine
CRP	C-reactive protein
CTGF	Connective tissue growth factor
CVS	Cardiovascular
CXR	Chest X-ray
DcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusion capacity for carbon monoxide
ESR	Erythrocyte sedimentation rate

EUSTAR	European League Against Rheumatism Scleroderma Trials and Research Group
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GIT	Gastrointestinal
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRCT	High resolution computed tomography
IFN-γ	Interferon-γ
IL-6	Interleukin-6
ILD	Interstitial lung disease
IQR	Interquartile range
KL-6	Krebs von den Lungen-6
LcSSc	Limited cutaneous systemic sclerosis
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume
MHC	Major histocompatibility complex
NSIP	Non-specific interstitial pneumonia

OR	Odds ratio
PAH	Pulmonary arterial hypertension
PDGF	Platelet-derived growth factor
PFT	Pulmonary function tests
RANTES	Regulated on activation normal T-cell expressed and secreted
RNP	Ribonucleoprotein
RNAP	Ribonucleic acid polymerase
ROS	Reactive oxygen species
SP-D	Surfactant protein D
SRC	Scleroderma renal crisis
SSc	Systemic sclerosis
TGF-β	Transforming growth factor -β
UIP	Usual interstitial pneumonia
Ur	Urea
WCC	White cell count

CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1.1 Overview of Systemic Sclerosis

Systemic sclerosis (SSc) is a rare multi-system connective tissue disease. It is characterised by progressive fibrosis of the skin and internal organs, vasculopathy, and disease-specific autoantibodies[1-3]. It is broadly divided into two types: limited cutaneous SSc (lcSSc), where the skin fibrosis is limited to the distal extremities and face; and diffuse cutaneous SSc (dcSSc), where the fibrosis extends proximal to the elbows and knees and additionally involves the trunk[4]. The pattern of organ involvement in SSc frequently involves skin and lung, but may include the gastrointestinal tract, musculoskeletal system, cardiovascular system, and renal system. A more severe organ involvement is seen in those with dcSSc, compared to those with lcSSc. In Caucasian dominant populations such as in Europe and North America lcSSc is more common (56%) than dcSSc (34%)[5], whereas in African-American and Black populations the reverse is true, with rates of dcSSc of up to 82% being reported in Nigeria[6-9].

Systemic sclerosis is also known as scleroderma (literally “thickened skin” from Greek derivation) and was first described in detail by the dermatologist Carlos Curzio in 1752, although scholars believe reference is made to this condition in the writings of Hippocrates[10]. The term scleroderma was coined by Giovambattista Fontanetti in 1836[11], but it was not until 1945 that the systemic nature of the disease was highlighted by Robert Goetz, and the term systemic sclerosis (SSc) was more widely used[12]. The most “famous” of SSc patients was the Swiss artist Paul Klee (1879-

1940) (pictured in Figure 1.1.1 with clear SSc facies), who was diagnosed after his death following a 5-year aggressive disease course[13]. His artwork is featured on the logo for the European League Against Rheumatism Scleroderma Trials and Research Group (EUSTAR). His late work, shown in Figure 1.1.2, was created during his illness and clearly evokes the difficulties and suffering he experienced at the hands of SSc. Understanding of SSc has progressed dramatically since Klee's untimely demise, although many questions still remain.

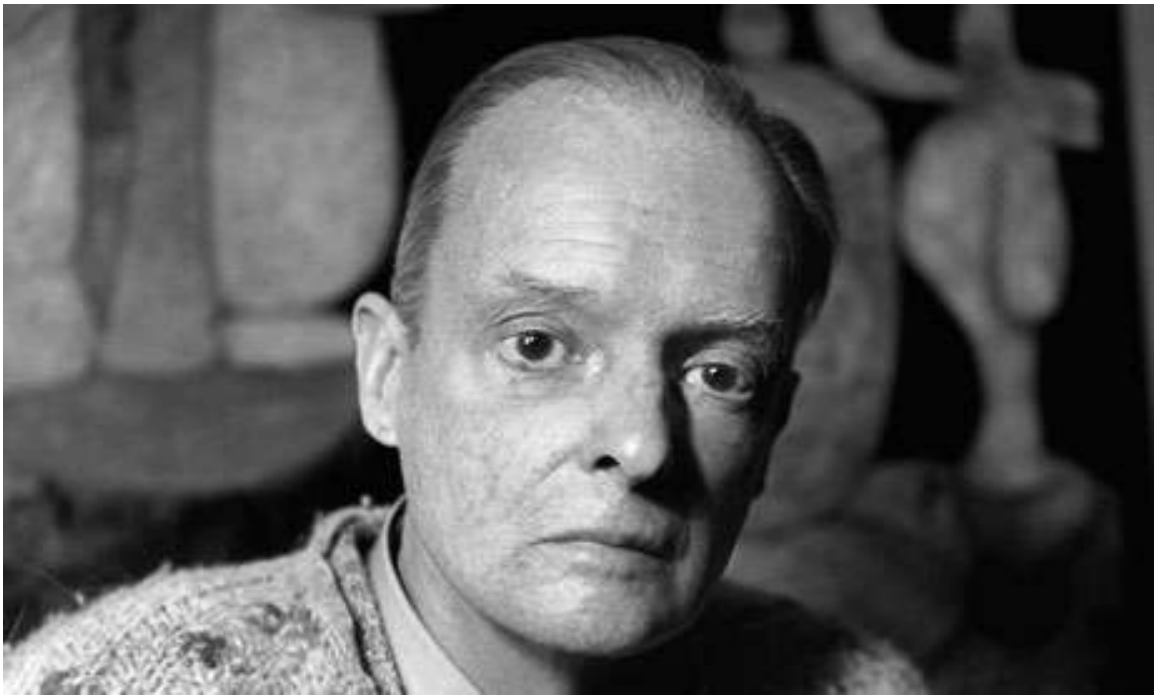

Figure 1.1.1 Artist Paul Klee, from a newspaper article in The Guardian [14]

Figure 1.1.2 "Angel applicant" by Paul Klee, 1939 [15]

The underlying cause of SSc is thought to involve a complex interplay between an initiating environmental trigger, individual genetic predisposition, and immune dysfunction[1]. It has an estimated worldwide prevalence between 50 and 300 per one million population. The incidence and prevalence varies geographically and amongst different ethnicities[1, 3, 16]. In a study carried out in South Africa at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, the average age of onset was 36 years[7], which is younger than described by other investigators where the peak age of onset was 45-55 years[17]. However, the ethnicity of the patients at CHBAH was exclusively Black, and world-wide African American patients with SSc are reported to present at a younger age and with more severe disease[2, 6, 18, 19]. SSc is four times more common in women than in men[17, 19].

Studies on genetic susceptibility suggest that HLA/MHC-associated loci and other non-associated loci are involved in the pathogenesis of SSc[20]. The HLA-associated gene *NOTCH4* has been linked to both SSc-specific antibodies: antitopoisomerase-I antibody (ATA) and anti-centromere antibody (ACA). The non-HLA associated gene *IRF8* has been linked to lcSSc and ACA [21]. Choctaw Native Americans have a unique HLA haplotype which is thought to confer SSc susceptibility[16]. These genetic associations may, with further elucidation, help to explain individual susceptibility to SSc, as well as help to explain the driving force behind associations between disease subtypes, laboratory features, and clinical outcomes, which are currently not clearly defined.

Multiple environmental factors have also been implicated in SSc, including silica, bleomycin, and vinyl chloride. In particular, silica exposure in gold-mining in men has been reported locally[22, 23], and internationally[24, 25] to increase the risk of developing SSc by a factor of between 3 and 28. Although cigarette smoking has not been linked to the development of SSc, it has been linked to disease severity[26].

Due to the association with autoantibodies, autoimmunity is thought to be involved in the pathogenesis of SSc. Antinuclear antibodies (ANAs) are positive in 75-95% of SSc participants with a sensitivity of 85% and specificity of 54%[27]. There are two main patterns of staining in ANA: speckled and nucleolar. Speckled patterns reflect ACA, and ATA, which are almost always mutually exclusive. Additionally anti-U1-ribonucleoprotein (RNP) and anti-RNA polymerase (RNAP)-II and -III give a speckled pattern. Nucleolar patterns of staining include anti-U3-RNP and RNAP-I.

The specific ANAs classically involved in SSc are ACA, ATA, and RNAP. These autoantibodies vary with disease subtypes, outcomes, and the population involved, although there is overlap. The ATA is very common (71%) in the Choctaw Native Americans[16], a population group with the highest rate of SSc worldwide. American Caucasian SSc patients are reported to have an ATA positivity of 21%[6]. In a South African study from 1991, of the 73 ANA positive Black SSc patients in Durban, 32% were ATA positive[28]. Anti-topoisomerase I antibody itself seems to be associated with dcSSc (occurs in 40%) as well as interstitial lung disease (ILD) (occurs in 45%), and confers a more severe disease process[6]. Anti-centromere antibody is more common in Caucasian patients (25% versus 7% in African Americans)[6], and in those patients with lcSSc (40-60%)[6, 29, 30].

As a multi-system disease the clinical presentation of SSc is variable. Almost all patients have skin thickening (up to 5% have sine SSc). In the initial stages of disease this may appear as a diffuse swelling of the hands and fingers, with arthralgia. Progression to skin thickening occurs in differing distributions depending on dcSSc and lcSSc patterns. Joint deformities can occur through skin tightening or contractures. Tendon friction rubs are more common in dcSSc and have been associated with organ involvement, particularly scleroderma renal crisis (SRC). Other skin manifestations include altered pigmentation (salt and pepper), calcinosis and telangiectasia[1-3]. Inflammatory arthritis may occur, as well as proximal weakness due to myositis.

Raynaud's phenomenon is the commonest feature in terms of the vasculopathy (>95%)[1], which may be severe enough to result in tissue ischaemia. This may be apparent on examination either as digital pulp loss, ischaemic pits, digital ulcers, or various capillary loop changes on nailfold capillaroscopy. Other common vasculopathies are pulmonary arterial hypertension (PAH), although pulmonary hypertension may be secondary to SSc ILD, and SRC.

Cardiac manifestations in SSc classically involve the myocardium with inflammation, ischaemia and fibrosis. This may lead to systolic and diastolic dysfunction, as well as arrhythmias resulting from disruption of the conduction system. Those with SSc are at higher risk of coronary vessel spasm. Pericardial disease also occurs including pericarditis, pericardial adhesions and pericardial effusions. Asymptomatic pericardial effusions are the most common, especially when associated with pulmonary hypertension, although tamponade can occur. Endocardial and valvular heart disease are rare[31]. In terms of indirect effects of SSc on the cardiac system, right heart failure may be secondary to ILD or PAH [1, 31].

Gastrointestinal effects in SSc are common, where oesophageal dysmotility and dilatation may present with dysphagia or dyspepsia. So-called "watermelon stomach" describes the endoscopic appearance of gastric antral vascular ectasia which usually causes anaemia. Diarrhoea and bloating are also common complaints in SSc, due to bacterial overgrowth of the small intestine, and may be complicated by nutritional abnormalities (vitamin B12 and folate deficiencies)[1].

Scleroderma renal crisis is a life-threatening manifestation of SSc which presents as acute malignant hypertension (although up to 10% of patients are normotensive) in the presence of microangiopathic haemolytic anaemia and renal failure. It is more common in those with tendon friction rubs, patients with rapidly progressive skin disease, those in the first 3 years of SSc diagnosis, those with anti-RNAP antibodies, and patients who have received high dose corticosteroids[1].

Lung involvement in SSc is diverse and includes: aspiration pneumonia (oesophageal reflux and dysmotility), bronchiectasis, medication-induced pneumonitis, pneumonia, pleural effusion, extrinsic restriction from chest wall skin fibrosis, neuromuscular weakness, pulmonary vascular disease, lung malignancy, and ILD[1]. SSc ILD itself is a rather heterogenous umbrella term that involves inflammation and fibrosis of the lung parenchyma, including non-specific interstitial pneumonia (NSIP) as well as usual interstitial pneumonia (UIP). NSIP occurs more frequently in SSc and is thought to represent an active inflammatory process, whereas UIP may be a "burnt out" fibrotic process[18, 32].

SSc is associated with a substantially poorer survival compared to the general population. As shown in Figure 1.1.3[33], leading causes of death have changed since the 1970s when SRC was by far the commonest. The reduction in SRC has come about through its treatment with the advent of angiotensin converting enzyme inhibitors. Among the leading causes of SSc related deaths currently are ILD and PAH; up to 42% of SSc patients with ILD die within 10 years of diagnosis[2, 33]. In

this context a better understanding of SSc ILD pathogenesis, natural history, progression, and an effective treatment are still sought.

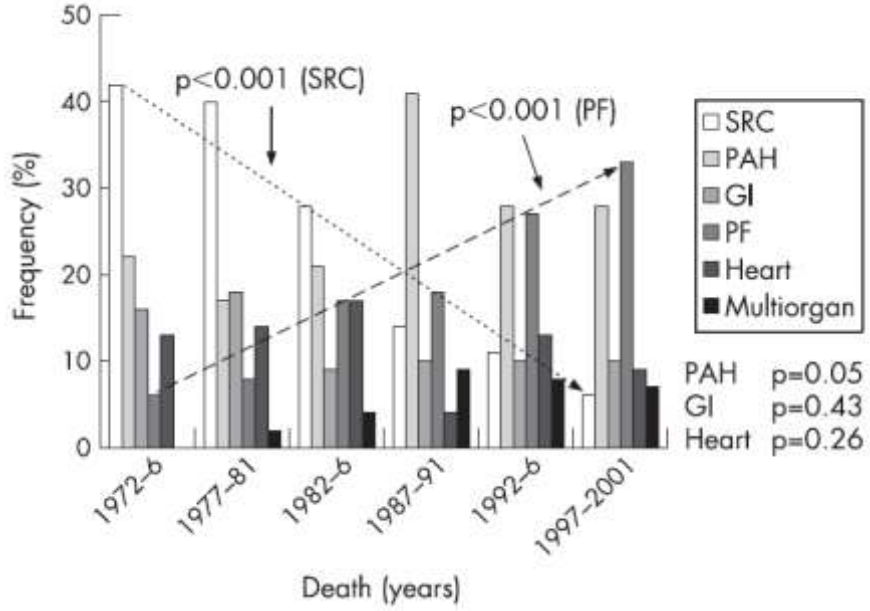

Figure 1.1.3. Causes of death in SSc over a forty year period, Steen et al (2007)[(33)]. SSc = systemic sclerosis; SRC=Scleroderma renal crisis; PAH = pulmonary arterial hypertension; GI = gastrointestinal; PF= pulmonary fibrosis.

1.2 Overview of interstitial lung disease in systemic sclerosis

The pathogenesis of SSc ILD has not yet been well elucidated, but the end-point is one of overproduction of extracellular matrix proteins by fibroblasts resulting in fibrosis, vasculopathy, and tissue ischaemia. This is thought to be caused by abnormal and dysregulated interactions between endothelial cells, fibroblasts, and immune cells (Figure 1.2.1). Endothelial cells secrete pro-inflammatory cytokines (Endothelin-1, Transforming Growth Factor Beta (TGF-β), and Platelet Derived Growth Factor (PDGF)), possibly in response to injury, which activate fibroblasts. The *NOTCH4* gene identified by Gorlova et al [(21)] in SSc patients has been

implicated in this TGF-β pathway, which may contribute to the initiation of endothelial secretion. Fibroblasts subsequently secrete interleukin-6 (IL-6) to activate T- and B-lymphocytes. T-lymphocytes promote a T-helper 2 response, predominantly through the secretion of interleukin-4 (IL-4), facilitating fibroblast proliferation and collagen synthesis. B-lymphocytes are responsible for autoantibody production, the pathogenic role of which is uncertain. There seems to be a reduced effectiveness in SSc patients of interferon-γ (IFN- γ) which normally acts as a potent suppressor of collagen synthesis by fibroblasts. There also appears to be a role for reactive oxygen species (ROS), and resultant oxidative stress as either an initiating or exacerbating factor for endothelial cells, fibroblasts, and immune cells[18].

Environmental factors associated with ILD include silica exposure in gold mining in men, which has been reported locally[22, 23], and internationally[2]. Cigarette smoking may be linked to ILD disease severity[2].

The specific ANA most frequently associated with SSc ILD is ATA (45%)[29], whereas ACA may be protective as it is associated with non-ILD SSc manifestations[7, 18]. In a 1999 South African study, Tager and Tikly[7] found a high cumulative occurrence of ATA (and lack of ACA) and ILD (56%) based on chest X-ray (CXR) findings in their exclusively Black participants, and that ILD was more common in those with dcSSc.

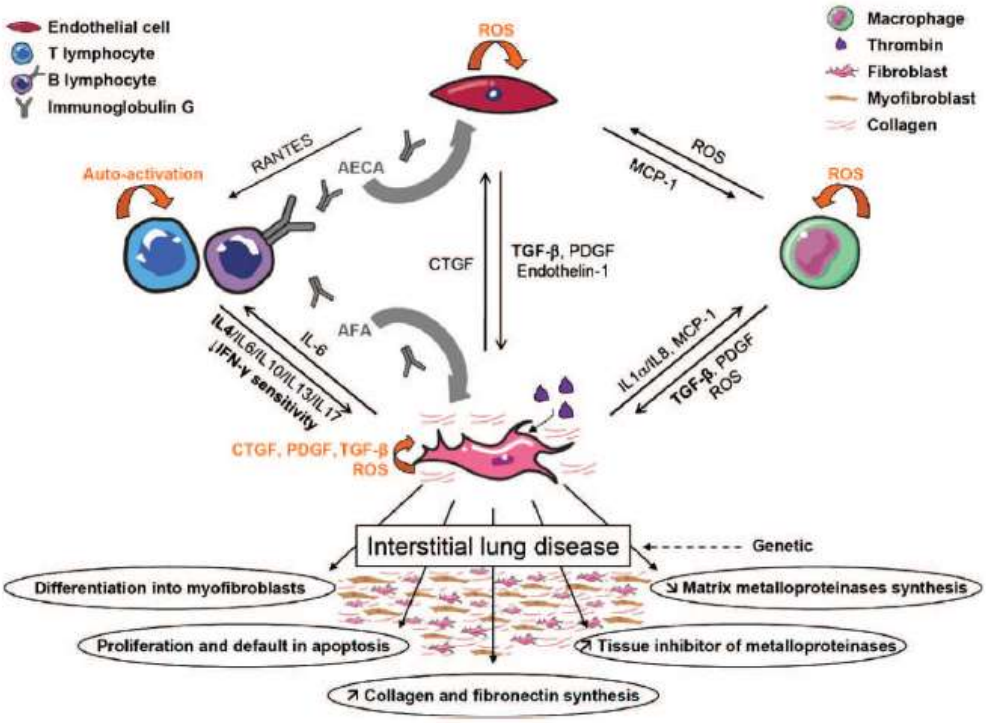

Figure 1.2.1 Pathophysiology of Systemic Sclerosis Interstitial Lung Disease (Bussonne et al [18]). AECA=anti-endothelial cell antibodies; AFA=anti-fibroblast antibodies; CTGF=connective tissue growth factor; IFN-γ=interferon gamma; IL=interleukin; MCP-1=monocyte chemoattractant protein-1; PDGF=platelet-derived growth factor; RANTES=regulated on activation normal T-cell expressed and secreted; ROS=reactive oxygen species; TGF-β=transforming growth factor beta.

Interstitial lung disease in SSc has a wide-ranging reported prevalence in the literature, from 16 to 91%[18, 34]. It is more common amongst male scleroderma patients, in contrast to the female predominance of SSc generally[1, 19, 35]. It occurs early in the SSc disease process: Solomon et al[32] reported that 25% of ILD patients were diagnosed with ILD within the first 3 years of SSc diagnosis; whereas Steen and Medsger[36] reported that 45-55% of severe ILD occurred in the first 3 years of SSc diagnosis. In addition, McNearney et al.,[37] reported that African American patients have a higher rate of ILD (46%) compared to White (19%) and Hispanic (25%) patients, as well as a more severe ILD as measured by pulmonary function tests (PFTs). Steen and colleagues[6] also reported a higher rate of ILD amongst

African American patients (52%) compared to White patients (11%), particularly those that were ATA positive (44% in African American SSc patients versus 18% Caucasian SSc patients). Diffuse cutaneous disease is also more common in African American patients and is in itself more commonly associated with SSc ILD (although it does still occur in lcSSc). Additionally, those with more extensive skin involvement are also more likely to develop ILD[38, 39].

The apparent discordance of data in the literature may be because SSc is a rare disease and the numbers of patients recruited are often insufficient to apply broader conclusions. Additionally, the methodology used to diagnose SSc ILD is not standardised. Methods used include: CXR; high-resolution computer tomography (HRCT); PFT; lung biopsy; and broncho-alveolar lavage (BAL) washing analysis, and post-mortem histological analysis. In the EUSTAR database of 7655 patients, the prevalence of ILD was found to be 32% by PFT, 40% by CXR and 52% by HRCT[40]. Some have reported that clinical examination and CXR alone is robust enough to diagnose ILD in SSc patients[34], however to follow the progression of SSc ILD or to monitor response to treatment, PFT (particularly forced vital capacity (FVC)) and HRCT are recommended[34]. Measures of prognosticating SSc ILD include BAL analysis, although this is less popular currently due to its invasive nature[39].

Patients with SSc ILD may complain of exertional dyspnoea, and a non-productive cough. However, patients are often asymptomatic, particularly in the early stages of disease[1, 3], when they are most likely to develop SSc ILD. On examination late inspiratory bibasal crackles may be found, although these can be difficult to

auscultate or absent in early disease. Additionally, signs of pulmonary hypertension and cor pulmonale in late stages of the disease. Routine investigations for ILD amongst newly diagnosed SSc patients have therefore been advocated[32, 41] which include CXR, PFT, and HRCT. Chest X-ray may be normal in early disease, but may show a predominantly basal interstitial opacification in a reticulonodular pattern; PFTs may demonstrate a restrictive lung disease and decreased diffusion capacity for carbon monoxide (DLCO); and HRCT may reflect a wide variety of changes including ground-glass opacification, reticulonodular opacities, honeycombing, consolidation, or traction bronchiectasis.

1.3 Interstitial lung disease treatment in systemic sclerosis

Systemic sclerosis ILD is treated with immunosuppressive agents. There is no "gold-standard" treatment protocol, and there are few double-blind randomized controlled studies in support of different agents. Much of the rationale behind treatment comes from therapies used for idiopathic pulmonary fibrosis[18]. A difficulty in the literature around SSc ILD treatment lies in the differing measurements for efficacy and different end-points, rendering application of this data problematic.

Hoyles et al., (2006)[42] required their study participants to have HRCT scans and lung biopsies prior to study recruitment, and measured improvement in FVC and DLCO to reflect improvement of ILD. With their treatment of corticosteroids and intravenous cyclophosphamide, followed by maintenance oral azathioprine, there was a modest trend in improvement in lung function at 1 year. Tashkin et al.,

(2007)[43], as part of the Scleroderma Lung Study, recruited SSc participants with evidence of active ILD on HRCT, with or without BAL results. They found the benefits of oral cyclophosphamide treatment (as measured by FVC, DLCO, skin scores, and dyspnoea indices) were temporary, so that the beneficial effects of the treatment regime disappeared within a year of stopping treatment.

Some of the studies reviewed by Matucci-Cerinic et al., (2007)[44] and Nannini et al., (2008)[45], used stabilisation of FVC as an outcome measure rather than improvement of FVC, which appears to be achieved by both oral and intravenous cyclophosphamide regimes. In a local study, Dheda et al., (2004)[46] also found some success with stabilisation of lung function and improvement of dyspnoeic symptoms using azathioprine and low-dose corticosteroids. Additionally, there have been studies into the use of mycophenolate mofetil (MMF)[39], and rituximab[47], which seem to show similar results.

The fact remains, however, that most studies fail to show long-lasting significant improvements in FVC with treatment. Perhaps this is due to the failure to identify subsets of participants at risk of progression, as well as those most likely to respond to treatment.

1.4 Interstitial lung disease severity and progression in systemic sclerosis

Patients who present with severe ILD (baseline FVC<50% predicted), and who have a progressive decline (of more than 10%) in FVC in the first year of symptom onset, appear to have a more aggressive course and higher mortality rate[18, 48-50]. African American patients have a more severe ILD (32% severe ILD in African American patients versus 13% severe ILD in Caucasian patients)[6] with a higher mortality rate compared to matched Caucasian patients[6, 32, 50]. In fact, the hazard ratio of 1.68 (95% CI 1.30-2.16, p<0.0001) assigned to African American ethnicity was the most significant among all hazardous variables reported by Steen and Medsger[6]. Others that were less significant include: age at first visit, male gender, and dcSSc.

Goh et al (2008)[41], suggested an algorithm for grading of SSc ILD (Figure 1.4.1) whereby both HRCT and FVC severity are used to classify ILD into extensive and limited disease. This was aimed at guiding clinicians on when to initiate treatment, and for which patients. Those with extensive disease (>20% ILD on HRCT, and FVC<70%) should be treated, whilst those with limited ILD (<20% ILD on HRCT, and FVC≥70%) should be monitored. Solomon and colleagues[32] then adapted this algorithm (Figure 1.4.2) to suggest a protocol for following up SSc ILD patients: those with limited ILD should monitored every 3-6 months for progression; and those without any evidence for ILD should be monitored with yearly PFTs.

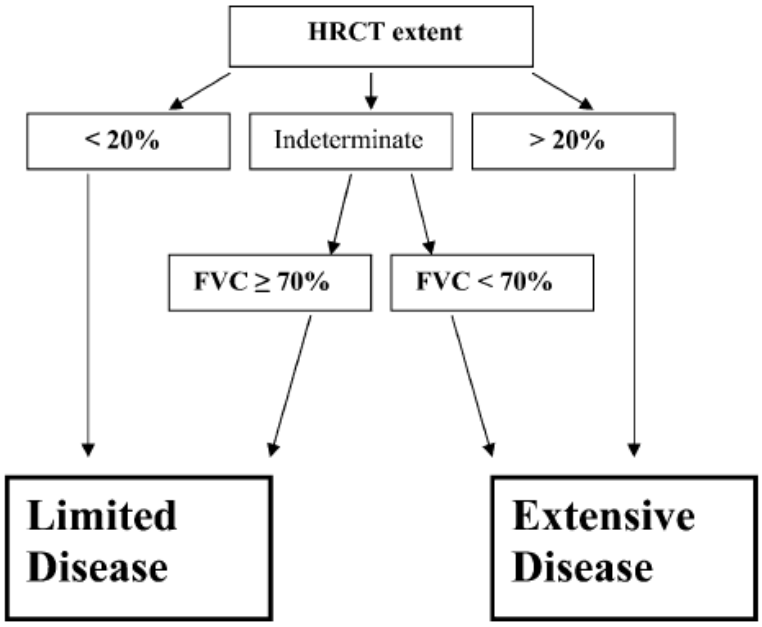

Figure 1.4.1 Algorithm for the initiation of treatment of SSc ILD (Goh and colleagues, 2008[41])

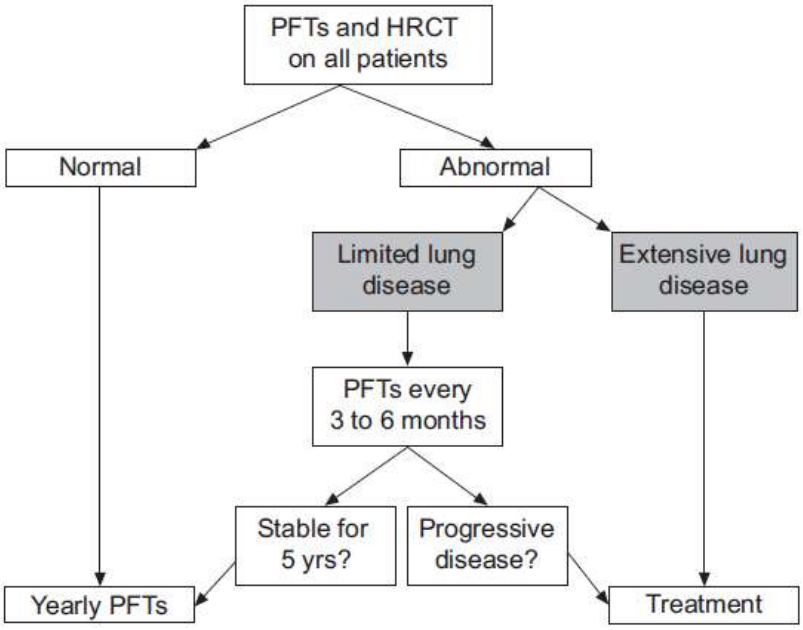

Figure 1.4.2 Algorithm for follow up of SSc ILD patients (Solomon et al., 2013[32])

Of interest in resource-poor settings, where HRCT (and possibly PFTs) may not be readily available, is the correlation between severity of lung fibrosis with clinical

parameters at presentation - namely skin scores, dyspnoea and cough. Theodore et al., (2012)[51] found that cough correlated with severity of fibrosis, settled with treatment with cyclophosphamide, and returned with worsening disease activity. Assassi et al., (2010)[50], showed that in addition to a higher visual analogue score for dyspnoea, the presence of bibasal crackles on physical examination was associated with a poorer FVC at baseline. Roth et al., (2011)[52] found that the Mahler baseline dyspnoea index, and the modified Rodnan skin score were predictive of response to cyclophosphamide. Those with skin scores of more than 23 and those with more than 50% involvement on HRCT showed a mean improvement in FVC of 9.81% at 18 months from baseline with treatment.

Muangchan and colleagues (2012)[53] demonstrated that a baseline C-reactive protein (CRP) > 8 mg/litre was associated with "disease activity, severity, poor pulmonary function, and shorter survival." This was supported by Liu et al (2013)[54] who found that baseline CRP predicted progression in FVC decline, and is associated with shorter survival. Other serological markers of interest are: KL-6 (Krebs von den Lungen-6; a human mucin glycoprotein over-secreted by type II pneumocytes in SSc ILD patients); and SP-D (Surfactant protein D, also increased in SSc ILD patients compared to normal controls)[39]. However, neither KL-6 nor SP-D is available in the clinical setting as yet, whereas CRP is a widely used routine blood test in the setting of SSc.

Whether those who attend the CHBAH Connective Tissues Diseases Clinic are comparable to SSc ILD patients described in the literature outlined above in terms of

disease spectrum and natural history, has yet to be established. Particularly whether factors identified by other investigators could be applied to these patients in order to identify those at high risk of severe and progressive ILD to provide an early and effective intervention, is unknown.

1.5 Aim

To describe the profile of SSc ILD patients at the CHBAH Connective Tissue Diseases Clinic from 1 January 1992 until 31 May 2012, in order to better understand SSc ILD in South Africans.

1.6 Objectives

1. To determine the prevalence and spectrum of ILD in SSc patients and to describe the associations with baseline demographic, clinical and laboratory features.
2. To determine the severity and progression of ILD in SSc patients and to describe associations with baseline demographic, clinical and laboratory features.
3. To determine outcomes of treatment response for SSc ILD in terms of any significant changes from baseline FVC, and to determine baseline factors that could predict response.
4. To determine survival among SSc ILD participants, and to identify any baseline variables that are associated with mortality.

CHAPTER TWO: PATIENTS AND METHODS

2.1 Study design

A single-centre retrospective observational study of adult patients with SSc ILD at the Connective Tissue Diseases Clinic at CHBAH. Inclusion criteria included: age ≥ 18 years; all patients with SSc registered at the Connective Tissue Diseases Clinic, CHBAH, from 1 January 1992 until 31 May 2012; all patients met the American College of Rheumatology preliminary classification criteria for SSc [55] (Appendix A); adequate records with respect to HRCT and PFT. The only exclusion criterion was inadequate records. Ethical approval was granted from the Human Research Ethics Committee (Medical) at the University of Witwatersrand (Appendix C).

2.2 Data collection

Data was retrieved from clinic files from patients presenting from 1 January 1992 until 31 May 2012. A data collection sheet was used (Appendix B) to record demographical, clinical assessments, laboratory data, and investigations at initial presentation. Additionally, treatment received over the course of the disease duration was noted, as well as overall survival. In terms of survival, it was recorded whether patients were known deceased, alive, or had been lost to follow up. Cause of death was documented as infection, malignancy, ILD, cardiovascular, or unknown. Cardiovascular causes of death included myocardial infarction, cardiomyopathy, and heart failure, or complications thereof. Age at SSc diagnosis was defined as the age in years at diagnosis of SSc by a rheumatologist. Duration of disease was defined as time in years from diagnosis until either last clinic appointment, or date of confirmed

death. Smoking history was judged to be positive if the participant had smoked at any stage (either previously or currently). Digital lesions (digital ulcers, scars, or gangrene) were grouped together as indicative of cutaneous vasculopathy. Nailfold changes were documented as dilated capillary loops, haemorrhages, or capillary drop out. Disease classifications were either diffuse cutaneous, limited cutaneous, based on descriptions by LeRoy and colleagues[4]. Unclassified SSc was allocated to those participants where there was insufficient data for classification (early SSc or sine SSc), or where an overlap syndrome existed (SSc overlapping with rheumatoid arthritis, for example).

SSc ILD was defined based on features of ILD on HRCT (groundglass opacification, fibrosis, and honeycombing) as judged by a pulmonologist or radiologist, with or without restrictive PFTs. High resolution computed tomography was ordered for all patients where ILD was suspected on clinical grounds (symptoms, bibasal crackles on examination, suggestive CXR or PFTs). The ILD diagnosis was recorded as a cumulative event. Pulmonary function tests were defined as restrictive if FEV1:FVC > 80% and impaired if FVC < 70% that of predicted, in line with Goh et al (2008) [41]. Impairment of FVC was classified as mild if FVC≥70%, moderate if FVC 50-69%, and severe if FVC<50%. Pulmonary function tests were collected at baseline (at the time of ILD diagnosis), and at 6 months, 1 year, and 2 years from baseline. Treatment response was classified as:

- *Improved* if FVC increased by >10% from baseline
- *Stable* if FVC remained within 10% of baseline
- *Worsened* if FVC declined by >10% from baseline

As such, participants who stabilised or improved were classified as having non-progressive ILD, and those who worsened were classified as having progressive ILD.

2.3 Data analysis and statistical methods

All the data collected using the data sheet (Appendix B) was entered into a database using Microsoft Excel. Appropriate descriptive analyses were performed on the demographic, clinical, and laboratory characteristics of all patients with SSc. Continuous data was tested for normality, and when found not to be normally-distributed, was converted using a logarithmic scale. Continuous data was expressed as means (± standard deviation (*SD*)) or medians (interquartile range (*IQR*)), the latter being used when the SD was greater than the mean. Categorical data was expressed as percentages.

Comparisons were made between participant groups using the 2-tailed Fisher's exact test for frequency data as *n* was often less than 5. For any frequency data larger than a 2x2 contingency table one-way ANOVA was used. The 2-tailed unpaired Student's *t*-test was used for quantitative data comparisons. A $p<0.05$ was considered statistically significant. The computation of odds ratios was done using a binary logistical option at a 95% confidence interval for all odds ratios. Multivariate logistical regression analysis was applied using the ENTER method[56] with all variables pre-determined from significance. The entry point was at $p=0.05$ and the exit point was at $p=0.10$.

CHAPTER THREE: RESULTS

3.1 Characteristics of overall systemic sclerosis cohort

A total of 177 patient files were examined, 151 of whom met the inclusion criteria. As such, 26 participants were excluded due to incomplete records or a diagnosis other than that of SSc (systemic lupus erythematosis, morphea, eosinophilic fasciitis). The overall findings for all participants at presentation are shown in Table 3.1.1. The majority of SSc participants were female (87.4%), and of Black ethnicity (86.2%). The remaining 13.8% of the patients were made up of Caucasian (2.7%), mixed race (0.7%), and Indian (3.3%) ethnicities. In 6.6% of patients ethnicity was not specified. The mean age (*SD*) at diagnosis was 44.1 years (*13.0*). The most common clinical findings were Raynaud's phenomenon (82.8%) and nailfold changes (70.2%), with the most common disease subtype being diffuse cutaneous (62.2%).

The average values (either mean or median, as appropriate) for blood tests in terms of urea (Ur), creatinine (Cr), white cell count (WCC), haemoglobin (Hb), mean cell volume (MCV), platelets, albumin (Alb), were all within normal ranges. Seventeen participants (11.3%) had renal impairment with Cr>100mmol/l at presentation, 49 (32.5%) were anaemic with Hb<12g/dl, 8 (5.3%) had leukopaenia (WCC<4.0x10^9/l), 4 (2.6%) had thrombocytopaenia (<100 x 10^9/l), 65 (49.6%) had hypoalbuminaemia of less than 40g/l, and roughly half of the participants had raised inflammatory markers (CRP and ESR, erythrocyte sedimentation rate). Nine participants (6.0%) were HIV positive. There was insufficient data to allow meaningful description or

analysis for vital signs, height, weight, Rodnan skin scores, urine analysis, echocardiogram, chest X-ray, barium swallow or gastroscopy.

Table 3.1.1 Overall baseline features of all systemic sclerosis participants

Demographics	**n=151 (%)***
Female:Male	7:1
Mean age at diagnosis in years *(SD)*	44.1 *(13.0)*
Median duration in years *(IQR)*	4.0 *(6.0)*
Black ethnicity	131 (*86.2*)
History	
Gold-mining history	6 *(4.0)*
Smoking history *(n=130)*	20 *(15.4)*
Raynaud's phenomenon	125 *(82.8)*
Reflux	85 *(56.3)*
Proximal weakness	56 *(37.1)*
Arthralgia	90 *(59.6)*
Dyspnoea	52 *(34.4)*
Cough	*37 (24.5)*
Examination	
Digital lesions	66 *(43.7)*
Nailfold changes	106 *(70.2)*
Telangiectasia	19 *(12.6)*
Calcinosis	13 *(8.6)*
Arthritis	33 *(21.9)*
Tendon friction rubs	15 *(9.9)*
Proximal Myopathy	56 *(37.1)*
Scleroderma renal crisis	3 *(2.0)*
Bibasal crackles	39 *(25.8)*
Disease subtype	
Diffuse cutaneous systemic sclerosis	94 *(62.2)*
Limited cutaneous systemic sclerosis	46 *(30.5)*
Unclassified systemic sclerosis	11 *(7.3)*
Laboratory Features	
Renal dysfunction (Cr>100mmol/l)	17 *(11.3)*
Leukopaenia (WCC<4.0x10^9/l)	8 *(5.3)*
Anaemia (Hb<12.0g/dl)	49 *(32.5)*
Thrombocytopaenia (<100 x 10^9/l)	4 *(2.6)*
Hypoalbuminaemia (<40 g/l) (n=131)	65 *(49.6)*
HIV positive	9 *(6.0)*
CRP > 8mg/l	61 *(40.4)*
ESR >20 mm/hr	83 *(55.0)*

HIV=human immunodeficiency virus; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; Cr=creatinine; Hb=haemoglobin; WCC=white cell count; * (%) unless otherwise stated.

As demonstrated in Table 3.1.2, the majority of participants were ANA positive (88.1%). Of those who were ANA positive, the most common ANA patterns were speckled (40.6%) and nucleolar (31.6%). Anti-topoisomerase I antibody was present in 18.8% of participants while only 7.5% of participants had a positive ACA. Interestingly, 24.4% of those who had dcSSc were ATA positive whereas only 5.4% of lcSSc participants were ATA positive (p=0.021). In contrast, 21.6% of those who had lcSSc were ACA positive whereas only 1.1% of those who had dcSSc were ACA positive (p<0.001).

Table 3.1.2. Autoantibody profiles in overall group and systemic sclerosis subtypes

Anti-nuclear antibodies	**Overall (n=151)**	**Diffuse cutaneous (n=94)**	**Limited cutaneous (n=46)**	***p***
Positive ANA *(%)*	133 *(88.1)*	87 *(91.5)*	37 *(80.4)*	ns
Speckled ANA pattern *(%)*	54 *(40.6)*	33 *(38.4)*	17 *(45.9)*	ns
Homogenous ANA pattern *(%)*	4 *(3.0)*	2 *(2.3)*	1 *(2.7)*	ns
Nucleolar ANA pattern *(%)*	42 *(31.6)*	30 *(34.9)*	9 *(24.3)*	ns
Anti-centromere antibody *(%)*	10 *(7.5)*	1 *(1.1)*	8 *(21.6)*	<0.001
Anti-topoisomerase I antibody *(%)*	25 *(18.8)*	21 *(24.4)*	2 *(5.4)*	0.021

ANA=antinuclear antibodies; ns=not significant.

In terms of survival, approximately 40% of patients were lost to follow up, 45% were known to be alive, and 14.6% were confirmed to have died (see Table 3.1.3). The cause of death was known in 16 of the 22 participants who had died (72.7%). Infection (27.3%) was the commonest cause of death, followed by ILD (18.2%), cardiovascular (18.2%), and malignancy (9.1%).

Table 3.1.3 Overall survival of all systemic sclerosis participants

Outcome	n (%)
Lost to follow up	61 *(40.4)*
Alive	68 *(45.0)*
Demised	22 *(14.6)*
Cause of death (n=22): Infection	6 *(27.3)*
Unknown	6 *(27.3)*
ILD	4 *(18.2)*
Cardiovascular	4 *(18.2)*
Malignancy	2 *(9.1)*

ILD=interstitial lung disease

3.2 Associations of interstitial lung disease with demographic, clinical and laboratory features

Of the 151 participants evaluated, 60 (39.7%) were diagnosed with ILD based on HRCT findings, with or without PFTs. A total of 56 ILD patients had HRCTs, 52 of whom had available reports. In the available HRCT reports, 26 participants (50.0%) had ground glass, 31 (59.6%) had honeycombing, and 12 (23.1%) had fibrosis, with 22 (42.3%) having a combination of these. There was only one patient (1.7%) who was unable to perform PFTs due to ill health, although due to lack of availability at the time 7 patients (11.7%) did not have full lung function at diagnosis, and 29 (49.2%) did not have full lung function at follow up. No participants had lung biopsies performed.

In the ILD group there was a longer median disease duration (6.2 years versus 4.0 years; *p*=0.009) (Table 3.2.1). The majority of ILD patients (63.3%) were diagnosed with ILD the same year as their SSc diagnosis, and 73.3% within 3 years of their SSc diagnosis.

Table 3.2.1 Baseline features in ILD and non-ILD participants

Demographics	**ILD (n=60) (%)***	**Non ILD (n=91) (%)***	***p***
Female:Male	5:1	9:1	ns
Mean age at diagnosis in years *(SD)*	42.7 *(12.1)*	45.0 *(13.4)*	ns
Median duration in years *(IQR)*	6.1 *(8.3)*	4.0 *(5.0)*	0.009
Black ethnicity	53 *(88.3)*	78 *(85.7)*	ns
History			
Gold mining history	5 *(8.3)*	1 *(1.1)*	0.037
Smoking history	8 *(15.7) (n=51)*	11 *(13.8) (n=80)*	ns
Raynaud's phenomenon	50 *(83.3)*	74 *(81.3)*	ns
Reflux	33 *(55.0)*	51 *(56.0)*	ns
Proximal weakness	24 *(40.0)*	32 *(35.2)*	ns
Arthralgia	37 *(61.7)*	52 *(57.1)*	ns
Dyspnoea	27 *(45.0)*	24 *(26.4)*	0.014
Cough	21 *(35.0)*	15 *(16.5)*	0.007
Examination			
Digital lesions	24 *(40.0)*	42 *(46.2)*	ns
Nailfold changes	39 *(65.0)*	66 *(72.5)*	ns
Telangiectasia	6 *(10.0)*	13 *(14.3)*	ns
Calcinosis	7 *(11.7)*	5 *(5.5)*	ns
Arthritis	14 *(23.3)*	19 *(20.9)*	ns
Tendon friction rubs	4 *(6.7)*	11 *(12.1)*	ns
Proximal Myopathy	19 *(31.7)*	36 *(39.6)*	ns
Scleroderma renal crisis	1 *(1.7)*	2 *(2.2)*	ns
Bibasal crackles	28 *(46.7)*	10 *(11.0)*	<0.0001
Disease subtype			
Diffuse cutaneous systemic sclerosis	49 *(81.7)*	45 *(48.9)*	<0.001
Limited cutaneous systemic sclerosis	8 *(13.3)*	38 *(41.3)*	<0.001
Unclassified systemic sclerosis	3 *(5.0)*	8 *(8.7)*	ns
Laboratory Features			
Renal dysfunction (Cr >100 mmol/l)	4 *(6.7)*	13 *(14.3)*	ns
Leukopaenia (<4.0 x 10^9/l)	2 *(3.3)*	6 *(6.6)*	ns
Anaemia (Hb<12.0g/dl)	20 *(33.3)*	29 *(31.9)*	ns
Thrombocytopaenia (<100 x 10^9/l)	4 *(6.7)*	0 *(0.0)*	0.023
Hypoalbuminaemia (<40 g/l)	29 *(48.3)* (n=55)	36 *(23.8) (n=76)*	ns
HIV positive	4 *(6.8)*	5 *(5.5)*	ns
CRP > 8mg/l	26 *(49.1) (n=53)*	35 *(44.3) (n=79)*	ns
ESR >20 mm/hr	34 *(57.6) (n=59)*	47 *(54.7) (n=86)*	ns
Autoantibodies			
Positive ANA	57 *(95.0)*	76 *(83.5)*	0.065
Speckled ANA pattern	29 *(50.9)*	25 *(32.9)*	0.010
Homogenous ANA pattern	3 *(5.3)*	1 *(1.3)*	ns
Nucleolar ANA pattern	13 *(22.8)*	29 *(38.2)*	ns
Anti-centromere antibody	0 *(0.0)*	10 *(13.2)*	0.006
Anti-topoisomerase I antibody	13 *(22.8)*	12 *(15.8)*	ns

ILD=interstitial lung disease; IQR=interquartile range; SD=standard deviation; ns=non-significant; HIV=human immunodeficiency virus; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; ANA=anti-nuclear antibodies; * = (%) unless otherwise stated.

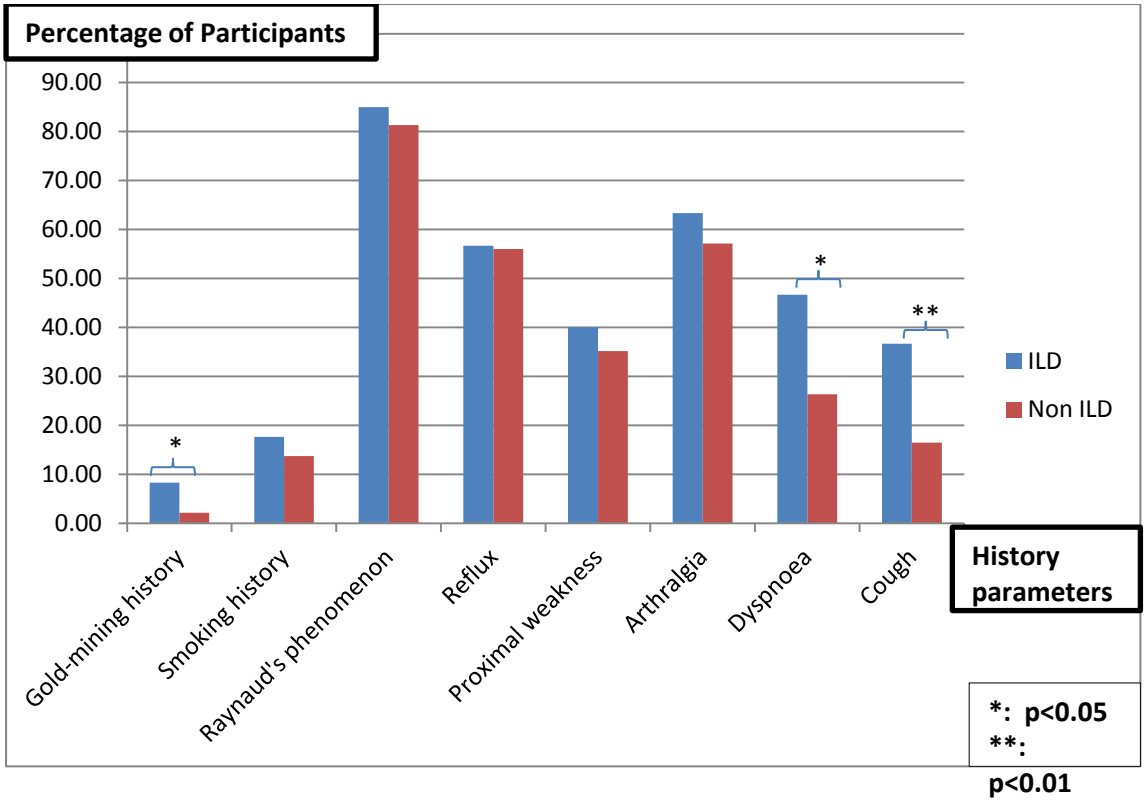

Figure 3.2.1 History findings of ILD and non-ILD participants. ILD = interstitial lung disease

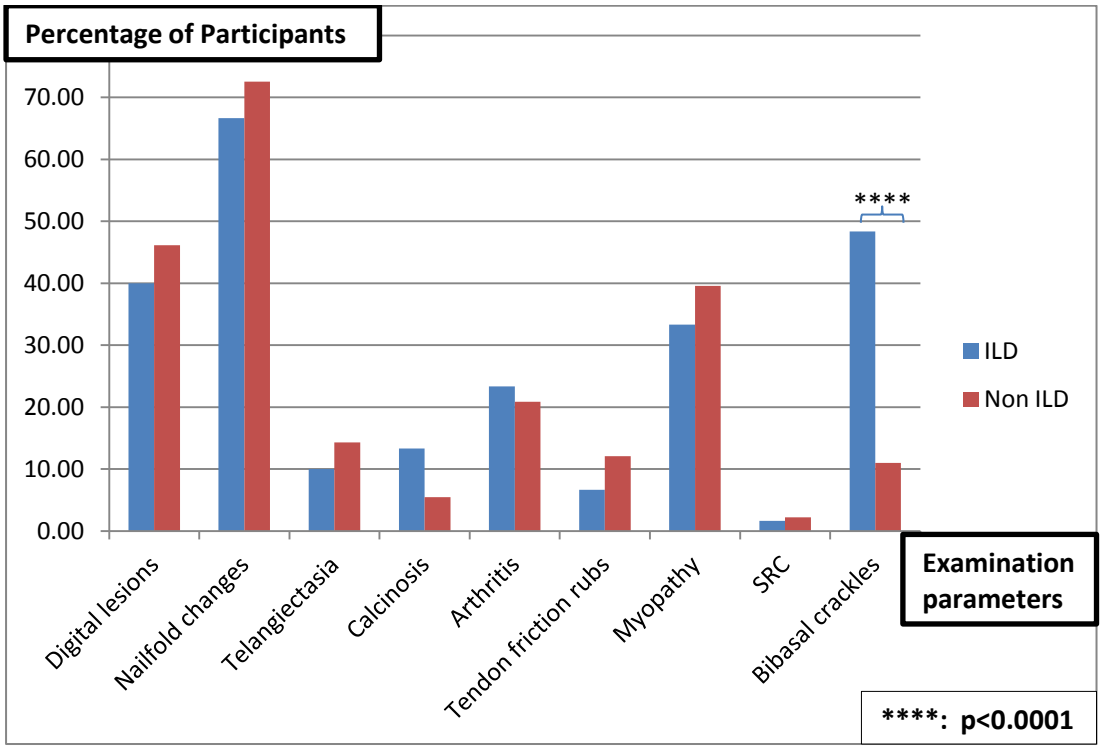

Figure 3.2.2 Examination findings of ILD and non-ILD participants. ILD= interstitial lung disease; SRC=scleroderma renal crisis.

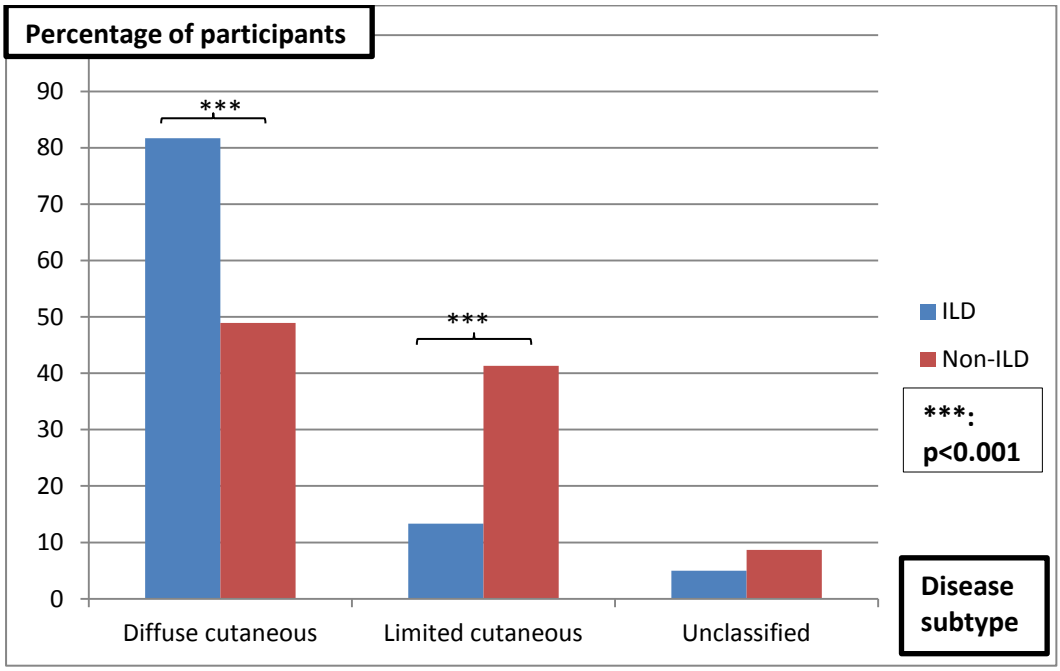

Figure 3.2.3 Disease subtype in ILD and non-ILD participants. ILD = interstitial lung disease.

In terms of participant history at presentation, the only significant associations at presentation with SSc ILD were Gold-mining history (p=0.037), dyspnoea (p=0.014), and cough (p=0.007), as shown in Figure 3.2.1. The only examination finding at presentation that showed a significant association with ILD was bibasal crackles (p<0.0001), as demonstrated in Figure 3.2.2. The dcSSc disease subtype was associated with the ILD group (81.7% versus 48.9% in non-ILD patients; p<0.001), whereas the lcSSc was associated with the non-ILD group (41.3% versus 13.3% in the ILD group; p<0.001).

In terms of laboratory results there were no significant differences between the average (either mean or median, as appropriate) values for ILD and non-ILD groups for full blood counts, urea and creatinine, inflammatory markers, albumin, and HIV

status. All the participants with thrombocytopaenia were in the ILD group (6.7% versus 0%; p=0.023). The clinical significance of this is unclear as none of these participants were HIV positive or had overlap disease.

On anti-nuclear antibody results, a positive ANA trended toward significance in the ILD versus non-ILD group (95.0% vs 83.5% respectively; *p*=0.065). The ANA pattern and specific autoantibodies did show significant differences between the ILD and non-ILD groups, as illustrated in Table 3.2.1 and Figure 3.2.4. The speckled ANA pattern was commoner in the ILD group (50.9% versus 32.9% in non-ILD group; *p*=0.010). In contrast, ACA was less common in the ILD group (0% versus 13.2% in the non-ILD group, *p*=0.006). In other auto-antibody testing (anti double-stranded DNA, anti-Ro, anti-La, anti-Smith, and anti-RNP), there were no significant differences between ILD and non-ILD groups.

In the multivariate logistic regression analysis significant variables associated with ILD were entered simultaneously; p for entry 0.05, p for removal 0.10. The odds ratios with confidence intervals (CI) set at 95% are demonstrated in Table 3.2.2 and represent an r^2 of 0.499 (Negelkerke). The 95% CI for Gold-mining history, dyspnoea, cough, and disease subtype all spanned unity, whereas disease duration, bibasal crackles, and speckled ANA all showed a predictive relationship to SSc ILD. Due to the fact that ACA had a zero frequency in the ILD group, odds ratios could not be calculated, although a protective relationship was suggested in univariate analysis.

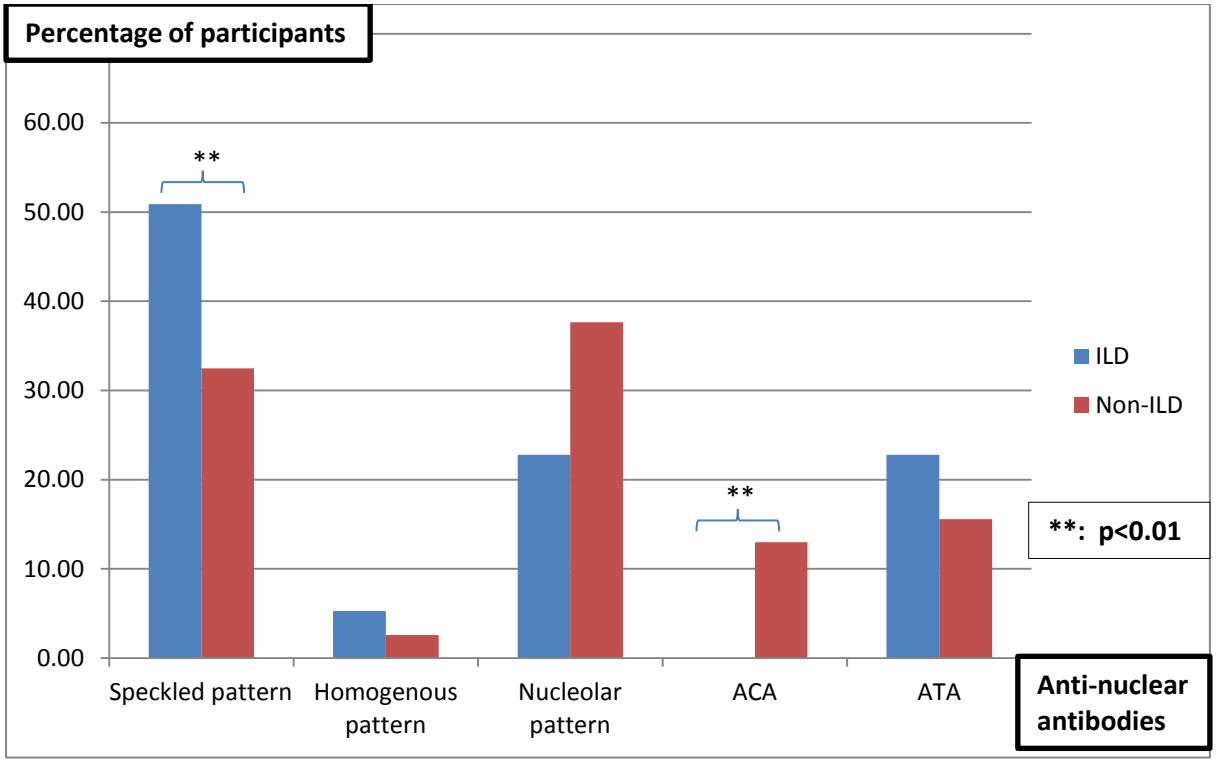

Figure 3.2.4 Autoantibodies in ILD and non-ILD participants. ILD = interstitial lung disease; ACA=anti-centromere antibody; ATA=anti-topoisomerase.

Table 3.2.2. Multivariate analysis for baseline predictors of ILD in systemic sclerosis

Variable	Odds ratio (95% confidence intervals)	*p*
Bibasal crackles	9.43 (3.25-27.39)	<0.0001
Disease duration	1.19 (1.09-1.30)	<0.0001
Speckled ANA	2.95 (1.22-7.15)	0.017
Gold mining	5.90 (0.49-70.78)	ns
Dyspnoea	1.05 (0.38-2.86)	ns
Cough	2.60 (0.86-7.87)	ns
Diffuse cutaneous disease	4.36 (0.79-24.23)	ns
Limited cutaneous disease	0.86 (0.14-5.26)	ns

ANA= anti-nuclear antibody. $r^2 = 0.499$

3.3 Interstitial lung disease severity in systemic sclerosis

Of the 60 ILD SSc participants, 59 were able to perform PFTs. The mean FVC % predicted (*SD*) at SSc ILD diagnosis was 78.4 (*22.1*). Participants were categorised

into mild ILD (FVC≥70%), moderate ILD (FVC 50-69%), and severe ILD (FVC<50%) at point of SSc ILD diagnosis. The mean FVC % predicted (*SD*) for each category were 98.0 (*17.5*), 66.2 (*8.0*), 38.0 (*12.1*) respectively. As there were only 3 participants with FVC<50%, moderate and severe ILD were grouped together. Thus the ILD group was subdivided into FVC≥70% (n=36; mean FVC 92.1%; SD 18.1) and FVC<70% (n=23; mean FVC 58.8%; SD 10.6). A comparative analysis was performed between these two severity subgroups to establish if there were any statistically significant associations with baseline variables.

The number of patients in the mild ILD group that were diagnosed in the same year as their SSc diagnosis was 19 (52.8%), whereas 17 (73.9%) of the moderate-severe ILD group were diagnosed in the same year of SSc diagnosis (p=0.013). The only variables at baseline that either trended toward significance or were significantly associated with ILD severity were amongst the history findings: those participants in the more severe ILD group had a higher percentage of participants with a history of gold mining (17.4 % vs 2.8% of participants in FVC≥70%), which trended towards significance (p=0.066); and those participants with more severe ILD were significantly associated with a history of dyspnoea at baseline (p=0.008).

3.4 Interstitial lung disease progression in systemic sclerosis

Of the 59 SSc ILD participants able to perform PFTs, 39 had follow-up PFTs at 6 months from ILD diagnosis. There was insufficient data for analysis at 1 year and 2 year follow-up PFTs. The 6-month follow-up PFT results were classified into those

that demonstrated a decline in FVC of greater than 10% (progressive ILD; n=9 (23.1%)), and those that demonstrated either an improvement or stabilisation in FVC within 10% of baseline (non-progressive ILD; n=30 (76.9%)). The mean baseline FVC % predicted (*SD*) for the non-progressive ILD group was 76.7 (*24.8*), and for the progressive ILD group was 80.8 (*20.2*). The mean FVC % predicted (*SD*) at 6 month follow-up in the progressive ILD group was 63.4 (*16.8*), with a mean decline in FVC % predicted (*SD*) of 21.2 (*8.4*) from baseline. There was no significant difference between progressive and non-progressive ILD groups in terms of time from SSc diagnosis to ILD diagnosis. A comparative analysis was performed between ILD progressive and ILD non-progressive participants to establish if there were any statistically significant associations between baseline variables and ILD progression at 6 months. There were no significant associations found.

3.5 Interstitial lung disease treatment in systemic sclerosis

The median time (*IQR*) taken from SSc diagnosis until SSc ILD diagnosis was 0 years (*1*). The median time (*IQR*) from SSc ILD diagnosis until SSc ILD treatment was 1 month (*3*). Of note is that 10 of the 60 SSc ILD participants were started on immunosuppression for other complications of SSc (severe skin disease, myositis, and others) prior to SSc ILD diagnosis. The data for both ILD subgroups, based on severity and progression, is displayed in Table 3.5.1.

Table 3.5.1 Time from systemic sclerosis diagnosis to interstitial lung disease diagnosis and treatment

	FVC≥70% (n=36)	FVC<70% (n=23)	*p*	Non-progressive ILD (n=30)	Progressive ILD (n=9)	*p*
Time from SSc diagnosis to SSc ILD diagnosis in years *(IQR)*	0 *(1)*	0 *(0.5)*	ns	0 *(1)*	0 *(2)*	ns
Time from SSc ILD diagnosis to SSc ILD treatment in months *(IQR)*	1 *(4)*	1 *(2)*	ns	1 *(3)*	4 *(4)*	ns

SSc=systemic sclerosis; FVC=forced vital capacity; ILD= interstitial lung disease.

As evidenced by the IQR values in *table 3.5.1*, there was a single participant in whom there was a delay of 85 months between ILD diagnosis and initiation of ILD treatment. This was because at ILD diagnosis the participant was asymptomatic and had UIP changes on HRCT, and therefore no treatment was given. Eighty-five months later this participant developed dyspnoea and NSIP changes on HRCT and was thus initiated on ILD treatment. Overall, there were no significant differences between the severity or progression ILD subgroups in terms of time to ILD diagnosis or time to ILD treatment.

The types of treatment administered to the ILD participants are shown in Table 3.5.2. Of the 60 SSc ILD participants, only 9 received no treatment for ILD (15.0%), the majority of whom were in the mild ILD and non-progressive ILD subgroups. Prior to the introduction of cyclophosphamide, D-penicillamine was used in the treatment of SSc ILD. Corticosteroids were used in conjunction with cyclophosphamide as an induction therapy followed by maintenance with either azathioprine or MMF. The

only significant difference between the two ILD subgroups in terms of treatment was that a higher percentage of patients in the non-progressive ILD subgroup received D-penicillamine (16.7% vs 11.1% in the progressive ILD subgroup, *p*=0.043).

Of the 51 SSc ILD participants who received treatment, only 7 (13.7%) developed complications during this treatment: 4 (7.8%) developed pulmonary tuberculosis; 2 (3.9%) developed haemorrhagic cystitis from cyclophosphamide; and 1 developed pneumonia (other than tuberculosis). There were no significant associations between ILD subgroups in this regard, as shown in Table 3.5.3.

Table 3.5.2 Interstitial lung disease treatments for subgroups

Treatment	**FVC≥70 % (n=36)**	**FVC<70 % (n=23)**	***p***	**Non-progressive ILD (n=30)**	**Progressive ILD (n=9)**	***p***
Intravenous Cyclophosphamide *(%)*	20 *(55.6)*	15 *(65.2)*	ns	21 *(70.0)*	5 *(55.6)*	ns
D-Penicillamine *(%)*	6 *(16.7)*	4 *(17.4)*	ns	5 *(16.7)*	1 *(11.1)*	0.043
Azathioprine *(%)*	11 *(30.6)*	5 *(21.7)*	ns	10 *(33.3)*	3 *(33.3)*	ns
MMF *(%)*	6 *(16.7)*	3 *(13.0)*	ns	3 *(10.0)*	4 *(44.4)*	ns
Methotrexate *(%)*	4 *(11.1)*	6 *(26.1)*	ns	3 *(10.0)*	1 *(11.1)*	ns
Corticosteroids (>10mg/day) *(%)*	26 *(72.2)*	18 *(78.3)*	ns	25 *(83.3)*	5 *(55.6)*	ns
No treatment *(%)*	6 *(16.7)*	2 *(8.7)*	ns	4 *(13.3)*	2 *(6.7)*	ns

FVC=forced vital capacity; ILD=interstitial lung disease; MMF= Mycophenalate mofetil.

Table 3.5.3. Complications during interstitial lung disease treatment

Complications	FVC≥70% (n=36)	FVC<70% (n=23)	*p*	Non-progressive ILD (n=30)	Progressive ILD (n=9)	*p*
Tuberculosis *(%)*	2 *(5.5)*	2 *(8.7)*	ns	2 *(6.7)*	1 *(11.1)*	ns
Other *(%)*	1 *(2.8)*	2 *(8.7)*	ns	2 *(6.7)*	0 *(0.0)*	ns

FVC=forced vital capacity; ILD=interstitial lung disease.

3.6 Interstitial lung disease survival in systemic sclerosis

The outcome of participants was recorded as: lost to follow up, alive, or deceased. Of the participants that were deceased, cause of death (if known) was recorded. There was insufficient data in this regard for any meaningful analysis. The results of ILD versus non-ILD participant outcomes are displayed in Table 3.6.1 and the ILD subgroup outcomes are displayed in Table 3.6.2. Approximately 40% of all participants were lost to follow up, and approximately 15% demised.

Table 3.6.1 Survival of ILD and non-ILD systemic sclerosis participants

Survival	ILD (n=60)	Non-ILD (n=91)	*p*
Lost to follow up *(%)*	25 *(41.7)*	36 *(39.6)*	ns
Alive *(%)*	26 *(43.3)*	42 *(46.2)*	ns
Deceased *(%)*	9 *(15.0)*	13 *(14.3)*	ns

ILD=interstitial lung disease.

The percentage of participants who died in the moderate-severe ILD group compared to the mild ILD group were similar (13.0% versus 16.7%; *p*=ns). However, the percentage of participants who died in the progressive ILD group was greater compared to the non-progressive ILD group (33.3% versus 10.0%; p=ns).

Table 3.6.2 Survival of ILD subgroup participants

Survival	FVC≥70% (n=36)	FVC<70% (n=23)	*p*	Non-progressive ILD (n=30)	Progressive ILD (n=9)	*p*
Lost to follow up *(%)*	14 *(38.9)*	10 *(43.5)*	ns	10 *(33.3)*	3 *(33.3)*	ns
Alive *(%)*	16 *(44.4)*	10 *(43.5)*	ns	17 *(56.7)*	3 *(33.3)*	ns
Deceased *(%)*	6 *(16.7)*	3 *(13.0)*	ns	3 *(10.0)*	3 *(33.3)*	ns

FVC= forced vital capacity; ILD=interstitial lung disease.

Of the 9 (15.0% of all ILD participants) ILD participants who were known to have demised, 4 (44.4%) died from ILD, 2 (22.2%) died from infections, and in a third of patients the cause of death was unknown. This contrasted to the non-ILD group where infection and cardiovascular were the joint leading causes of death (30.8%), followed by malignancy (15.4%). In the non-ILD group, 3 participants (23.1%) who died had no clear cause of death. These results are summarised in Table 3.6.3.

Table 3.6.3 Causes of death of ILD and non-ILD systemic sclerosis participants

Cause of death	ILD (n=9)	Non-ILD (n=13)	*p*
Infection *(%)*	2 *(22.2)*	4 *(30.8)*	ns
Malignancy *(%)*	0 *(0.0)*	2 (15.4)	ns
Cardiovascular *(%)*	0 *(0.0)*	4 *(30.8)*	ns
ILD *(%)*	4 *(44.4)*	0 *(0.0)*	0.017
Unknown *(%)*	3 *(33.3)*	3 *(23.1)*	ns

ILD=interstitial lung disease.

In order to identify any significant associations in the ILD group with those who had deceased, baseline variables were compared in ILD participants who were alive (n=26), and those ILD participants who were deceased (n=9). Those who were lost to follow up were excluded as their status in this respect was unknown. The

baseline variables that either trended toward significance or were statistically significant are shown in Table 3.6.4.

Table 3.6.4 Significant associations between presentation variables and ILD survival

Variable at presentation	ILD alive (n=26)	ILD deceased (n=9)	*p*
Median duration in years *(IQR)*	7.0 *(10.0)*	2.0 *(6.0)*	<0.0001
Proximal weakness *(%)*	9 *(34.6)*	2 *(22.2)*	0.035
Telangiectasia *(%)*	4 *(15.4)*	0 *(0.0)*	0.028
Bibasal crackles *(%)*	10 *(38.5)*	6 *(66.7)*	0.014
Diffuse disease subtype *(%)*	21 *(80.8)*	8 *(88.9)*	0.073
Mean Urea mmol/l *(SD)*	3.4 *(1.6)*	Median = 4.7 *(IQR: 1.9)*	0.041
Average Creatinine mmol/l	Mean = 60.4 *(SD=15.5)*	Median = 67.0 *(IQR=19.0)*	0.086
Mean Albumin g/l *(SD)*	39.1 *(3.5) (n=23)*	34.0 *(6.9)*	0.007
Median CRP in mg/l *(IQR)*	6.0 *(8.2) (n=21)*	9.2 *(40.8)*	0.066
CRP > 8mg/l *(%)*	7 *(33.3) (n=21)*	6 *(66.7)*	0.065

ILD=interstitial lung disease; CRP= C-reactive protein.

As demonstrated in Table 3.6.4, the median duration in years of SSc was significantly longer in ILD alive participants compared to ILD deceased participants (7.0 versus 2.0, respectively; $p<0.0001$). Proximal weakness was more often reported in alive ILD patients compared to those that died (34.6% versus 22.2%, $p=0.035$), as well as telangiectasia (15.4% versus 0%, $p=0.028$). Bibasal crackles at presentation was more common in ILD participants that died (66.7% versus 38.5%; $p=0.014$). Diffuse cutaneous SSc was more common amongst ILD participants who died (88.9% versus 80.8%, $p=0.073$), which trended toward significance.

In terms of blood test results, the average plasma urea was higher in the deceased ILD group (10.8 mmol/l versus 3.4 mmol/l in the alive ILD group, *p*=0.041), as was the average creatinine (157.8 mmol/l versus 60.4 mmol/l in the alive ILD group, *p*=0.086). This result may be affected by a single participant in the ILD deceased group that had SRC, as the median values between the two groups are comparable. The mean serum albumin was significantly lower in the ILD deceased subgroup compared to the ILD alive group (34.0 g/l versus 39.1 g/l; *p*=0.007). The median CRP was higher in the deceased group (9.2 mg/l versus 6.0 mg/l; *p*=0.066), and a higher proportion of participants in the deceased group had a CRP>8 mg/l (66.7% versus 33.3%; *p*=0.065), which trended towards significance.

On performing odds ratios on the above baseline variables with 95% confidence intervals using the ENTER method, all variables straddled unity and were thus not significant.

CHAPTER FOUR: DISCUSSION

4.1 Characteristics of overall systemic sclerosis cohort

There were 151 SSc participants in this study. The majority were female (7:1), and of Black ethnicity (>85%). The female predominance was more marked than previously reported both locally and internationally where a ratio of 4:1 was found. There may be an under-representation of male SSc patients in this study, but it is not clear why this would be. Numerically, the mean age at diagnosis was similar to the average age of onset in other studies which reported this to be 45-55 years[17]. However, these two concepts are not synonymous, making comparison difficult. Age of onset is prone to error in terms of recall bias, and onset of symptoms (Raynaud's or non-Raynaud's) are variably reported in the literature, hence the reason that age at diagnosis was used here. The age at diagnosis might be expected to be younger for a predominantly Black sample population as age of onset was reported to be younger internationally[6, 37]. This is likely to be explained by delayed presentation to the Connective Tissue Clinic at CHBAH either due to late presentation, or delays in referral due to failure by primary care practitioners to recognise features of connective tissue disease in younger patients.

The majority of participants had dcSSc (62%) which is in keeping with reported rates of 50-70% in African Americans[6, 19] and 66% in Black South Africans[7], and 57-82% of Black Africans[8, 9]. In contrast, diffuse cutaneous disease is described in only 37.1% of dominantly Caucasian patients in the EUSTAR cohort of 7655 scleroderma patients[40], which is a value consistent in the literature more generally where 30-40%

of Caucasian patients are reported to have dcSSc[5, 6, 19, 57]. The dcSSc subtype was more common amongst male participants (80% of the 19 male participants had dcSSc, and 60% of 132 female participants had dcSSc), although this was not statistically significant. This may be a function of the fact that males were under-represented in the sample population, and therefore the Gold-mining males may have skewed the male group towards the diffuse cutaneous disease subtype.

Common clinical features of the overall sample population were Raynaud's phenomenon (83%) and nailfold changes (70%). Raynaud's phenomenon has been reported more commonly in SSc participants (>95%) than has been found in this study[1], but it is a phenomenon that can be difficult to ascertain, especially in mild cases, and if there are language barriers as exists between patients and health care practitioners at CHBAH. Additionally, it is a sign that is more difficult to appreciate in pigmented skin. Nailfold changes reflect objective evidence of microvascular abnormalities with 70% of participants here demonstrating this sign.

A positive ANA was found in 88% of the 151 participants. A positive ANA has been reported in 75-95% of SSc patients in First World countries[27], with common patterns being nucleolar (anti-U3-RNP and RNAP I) and speckled (ATA, ACA, anti-U1-RNP, and RNAP-II and -III). The proportions of these antibodies depend upon the clinical phenotype of the group studied. For example, ACA is more common in lcSSc (40-60%) and Caucasian patients, and anti-U1-RNP and anti-U3-RNP are more common among African American SSc patients [6, 30]. The most common patterns found in this study were speckled (40.6%), nucleolar (31.6%) with ATA being the most

frequently measured specific autoantibody. Anti-topoisomerase I antibody was present in only 18.8% of SSc patients in agreement with local studies[7] and in contrast to findings in the EUSTAR dominantly Caucasian cohort of 36.8%[40]. Anti-centromere antibody was also quite uncommon with a rate of 7.5% amongst the ANA positive participants, which likely reflects the majority dcSSc disease subtype and Black ethnicity of this cohort. Indeed only 1 of the 87 ANA positive dcSSc participants were ACA positive whereas 21.6% of the 37 ANA positive lcSSc participants were ACA positive. Conversely 24.4% of the ANA positive dcSSc participants were ATA positive and only 5.4% of the ANA positive lcSSc participants were ATA positive. This significant association of ATA with dcSSc and ACA with lcSSC is consistent with published data [5, 6, 29, 58], however the number of lcSSc participants that were ACA positive is far fewer than reported in Caucasian dominant populations[1, 5, 19, 40], which is likely due to ethnic differences. The nucleolar ANA was a common pattern, but it unfortunately cannot be subtyped at CHBAH. One may suspect that it was contributed to by anti-U3-RNP, as this is a common antibody found in African American patients[30].

There was a high percentage of participants (approximately 40%) lost to follow up, which does not allow for meaningful interpretation of survival data. Some of these participants may have died, others may have defaulted follow up for any number of reasons. There were 22 (15%) patients known to have died, which is comparable to previously local data where a 13% mortality rate was reported[7]. In 27.3% of patients known to have died in this study, there was insufficient information to ascertain cause of death. In fact, there was only one documented post-mortem examination conducted where a cardiovascular cause of death was found. The lack

of information in this regard may be explained by noting that in many South African cultures post mortems are not acceptable to family members. From the data that does exist, ILD remains an important cause of death amongst the SSc patients at CHBAH, accounting for at least 18% of known deaths, and at least 44% of deaths in those with ILD. Despite limitations in terms of numbers lost to follow up, this is comparable to international data where ILD accounted for 16% of overall deaths[59].

4.2 Interstitial lung disease associations in systemic sclerosis

Interstitial lung disease in this study was common (40%). This is slightly lower than rates of ILD reported previously amongst African Americans internationally (46-52%)[6, 37]. The slight difference in ILD rate may lie in method of diagnosis. The rates in this study are however comparable to the EUSTAR database where 30-55% have been diagnosed with ILD by varying methods (40% by CXR, 32% by PFTs, 52% by HRCT)[40]. With regard to disease subsets, in this study 52.1% of dcSSc patients developed ILD whereas 64% of dcSSc patients in the EUSTAR database developed ILD[40], which is comparable. Meanwhile only 17.4% of lcSSc patients in this study developed ILD compared to 44% in the EUSTAR cohort[40]. The marked difference in proportions of lcSSc patients going on to develop ILD may be a function of cohort sizes (there are far more patients in the EUSTAR database), the lower proportion of lcSSc in this cohort (31% versus 59% in the EUSTAR database) likely due to ethnicity, and the lack of protective ACA in the lcSSc patients (and overall) in this study when compared to EUSTAR Caucasian predominant patients with lcSSc.

Of particular importance in this study was the comparative statistical association of SSc ILD with the following presentation features: dcSSc, history of Gold-mining, cough, dyspnoea, and bibasal crackles. Limited cutaneous SSc and ACA were associated with non-ILD participants. Based on the 95% confidence intervals of odds ratios on multivariate analysis, disease duration (OR 1.19; 95% CI 1.09-1.30), bibasal crackles (OR 9.43; 95% CI 3.25-27.39), and speckled ANA (OR 1.22; 95% CI 1.22-7.15) all showed predictive relationships to SSc ILD. As the 95% confidence intervals for the other variables (Gold-mining, cough, dyspnoea, disease subtype) all straddled unity, the odds ratios for these variables are of doubtful significance. This is likely a function of the limited numbers of participants. Although lcSSc was protective, the 95% confidence interval for the odds ratio for this variable crossed unity (OR 0.86; 95% CI 0.14-5.26). Due to the zero frequency of ACA in the ILD group, odds ratios could not be calculated for this protective variable. The generally wide confidence intervals are explained by the small numbers of participants for analysis.

The SSc ILD disease process seems to be driven by dcSSc, not ATA, and as such a number of SSc ILD associations may be linked to the diffuse cutaneous subtype:

- Participants with a Gold-mining history had a predominantly diffuse disease subtype (83.3%), and were almost six times more likely to develop ILD compared to those without a history of gold mining (OR 5.748, CI 95% 0.553-59.754, p=0.037).
- Diffuse cutaneous SSc itself was associated with SSc ILD (OR 2.257, CI 95% 0.464-10.969, p<0.001).

- Diffuse cutaneous was significantly associated with Scl-70 antibodies. These autoantibodies were not in turn associated with ILD, contrary to international data[6, 37].
- Those ILD participants who had deceased had a higher rate of dcSSc compared to ILD participants who were alive (88.9% vs 80.8%, *p*=0.073), which trended towards significance.

In terms of autoantibodies, a positive ANA trended towards significance in the ILD group, presumably due to a predominance of dcSSc in this group. As far as scleroderma specific autoantibodies are concerned, an association that has previously been reported is between ATA and SSc ILD[7, 18, 58]. In this study ATA was more common in participants with ILD (22.8% versus 15.6% in the non-ILD group), but not significantly so. Perhaps the lack of statistical significance was due to the limited numbers of participants, or it may be that this sample population is more comparable genetically to African American patients in Michigan where only 22% of Black patients were found to be ATA positive[19]. Another possibility is that ATA is more associated with dcSSc, rather than ILD in this cohort of patients. In support of this is the fact that 12 (24.5%) participants with dcSSc with ILD were ATA positive, and 9 (20.0%) participants with dcSSc without ILD were ATA positive. Also more common in the ILD group was the speckled ANA pattern (50.9% in ILD group versus 32.9% in non-ILD group; *p*=0.010), which may in part be attributed to anti-U1-RNP, more commonly found in African-Americans.

In contrast, ACA (0% in the ILD group versus 13.2% in the non-ILD group, *p*=0.006) and nucleolar-staining ANA patterns (22.8% in the ILD group versus 38.2% in the non-ILD group, *p*=ns) were less common in the ILD group. In fact, ACA was not found in a single ILD participant. Unlike with ATA, this does not seem to be a function of disease subtype in that none of the lcSSc participants with ILD (n=8) were ACA positive, whereas 8 (21.6%) of those lcSSc participants without ILD were ACA positive (*p*=ns). As previously mentioned, nucleolar antibodies cannot be subtyped at CHBAH, so the contribution of RNAP and anti-U3-RNP could not be demonstrated in participants with this ANA pattern. Interestingly, anti-U3-RNP has been shown to be more common in those with PAH, myositis and digital vasculopathy, and is more common in African American SSc patients[29, 30].

4.3 Interstitial lung disease severity in systemic sclerosis

The severity of ILD in this study was comparable to the spectrum of ILD seen in other studies, although there is some variation in the cut-offs used to define mild, moderate and severe ILD. The mild ILD participants represented 61.0% of the 59 ILD patients with PFTs at baseline, 33.9% had moderate ILD, and 5.1% had severe ILD at presentation. In the Pittsburgh database of 890 SSc patients, mild ILD was defined as FVC>75% predicted, moderate as predicted FVC of 50-75%, and severe as predicted FVC≤50%. Each category represented 60%, 27%, and 13% of ILD patients respectively[35]. The PFT cut-offs of 70% and 50% were used here to align with the Goh et al staging algorithm[41] (Figure 1.4.1). Other data published uses HRCT grading systems, which was not possible here as none of the HRCT scans were graded in terms of severity of ILD.

Significantly more patients with moderate-severe ILD were diagnosed with ILD in the same year as SSc. This may be considered compatible with data from Steen and Medsgar where the majority of severe SSc ILDs were diagnosed in the first 3 years of their SSc diagnosis[35]. It may, however, also be a function of late presentation, as well as those with more severe symptoms being fast-tracked for HRCT and PFTs.

The presence of dyspnoea at presentation was found to be significantly associated with ILD disease severity (FVC<70% predicted, p=0.008). These findings are consistent with previously reported international studies where cough was found to be a predictor of ILD activity and severity[51], and both dyspnoea and bibasal crackles were predictors of FVC decline in SSc ILD patients[52]. Unfortunately due to lack of data, particularly with respect to grading of ILD severity on HRCT, further associations were not amenable to analysis.

4.4 Interstitial lung disease progression in systemic sclerosis

Thirty nine (65.0%) out of the 60 ILD participants could be classified as having progressive ILD or non-progressive ILD based on PFTs at 6 months after SSc ILD diagnosis. The minority of these 39 participants (23.1%) progressed at 6 months from baseline. Those in the progressive ILD group demonstrated quite a dramatic decline in mean % predicted FVC (*SD*) over a 6 month period; from 80.8 (*21.2*) to 63.4 (*16.8*). Due to the lack of longitudinal data (6 month, 1 year, and 2 year PFTs) comparison with international literature is not possible. Another unfortunate casualty of the lack of adequate longitudinal data is that the impact of any intervention

(increasing the dose of cyclophosphamide or lengthening the duration of treatment) for the progressive ILD participants instigated at 6 months upon viewing a decline in FVC could not be evaluated.

There were no significant associations of baseline variables (demographic, clinical, or laboratory) with ILD disease progression, including baseline FVC. The lack of any associations may be due to the lack of data in that there were very limited numbers of ILD participants where follow up PFTs were performed. This was not done for 20 of the ILD participants (33%) as the PFT machine at CHBAH was not functioning for a number of years in the past decade and participants were referred to neighbouring hospitals for PFTs. Due to additional transport costs, and longer waiting lists due to increased strain on neighbouring hospitals' PFT machines, many participants were unable to attend such appointments.

In addition to missing data for PFTs, there was missing data for a number of baseline parameters. The lack of recording of modified Rodnan skin scores rendered analysis of these parameters non-representative, but would have been of particular interest as association between Rodnan skin scores and ILD progression has been reported previously[52].

4.5 Interstitial lung disease treatment in systemic sclerosis

The median time (*IQR*) in years from diagnosis of SSc to diagnosis of SSc ILD was 0 (*1*). This would suggest that most patients in this clinical setting were diagnosed with

SSc ILD at around the same time as first presentation to the Connective Tissue Diseases Clinic. The median time (*IQR*) in months from ILD diagnosis to ILD treatment was 1 (*3*), which reflects a prompt initiation of treatment within the department. The results were somewhat skewed by the 10 individuals who were started on immunosuppression (predominantly corticosteroids) prior to diagnosis of ILD. However there appears to be a similar counter effect whereby a single participant was started on treatment 85 months after ILD diagnosis as it was not until this late stage that he became symptomatic of ILD and showed changes on HRCT amenable to treatment.

Overall, approximately 85% of ILD participants received treatment with immunosuppression. The most frequently used medications were intravenous cyclophosphamide and corticosteroids. More of this regime was used in the non-progressive ILD group compared to the progressive ILD, but this was not statistically significant. The only significant difference shown in different treatment groups was an association between non-progressive ILD and the use of D-penicillamine (16.7% versus 11.1% in progressive ILD, p=0.043). This is consistent with data from Pittsburgh in 1985[60] where the use of D-penicillamine for SSc ILD was found to improve DLCO significantly, with no progression of dyspnoea symptoms. This was confirmed in 1987 in a smaller study by de Clerck et al[61], and more recently by Derk et al in 2001[62].

Complications occurring during treatment were restricted to 4 ILD participants (6.6%), and included infections (tuberculous and non-tuberculous), as well as

haemorrhagic cystitis from cyclophosphamide administration. This would be judged by most clinicians a good complication profile, although other side effects of medications reported by patients were not recorded in this study.

4.6 Interstitial lung disease survival in systemic sclerosis

There was no significant difference between ILD and non-ILD mortality rates (both approximately 15%). This may be due to the poor follow up rate, whereby about 40% of participants in each group were lost to follow up. The percentage of participants who died in the two ILD severity groups were similar (13.0% in the FVC<70% group versus 16.7% in the FVC≥70% group; *p*=ns). However, the percentage of participants who died in the progressive ILD group was greater compared to the non-progressive ILD group (33.3% versus 10.0%; *p*=ns). The lack of significance may lie in the small number of participants in these latter subgroups.

Associations with SSc ILD participant mortality were hampered by the low numbers of participants for whom this outcome was known. The high numbers of participants lost to follow up renders analysis, and application of this analysis difficult. Despite this, bibasal crackles was significantly associated with mortality in the ILD group (*p*=0.014), as were raised plasma urea (*p*=0.041) and reduced serum albumin (*p*=0.007). Interestingly, disease duration was shorter in those SSc ILD participants who had deceased compared to those that were alive (2.0 versus 7.0 years; p<0.0001). This would suggest those with a more aggressive ILD tended to develop ILD earlier in their SSc disease process. These findings are in keeping with those of

Steen and Medsger (2012)[36] who reported that 45-55% of severe ILD occurred in the first 3 years of SSc diagnosis. Proximal weakness and telangiectasia were significantly associated with ILD alive participants. This may reflect a tendency in these participants to muscle and vascular complications (as associated with nucleolar ANA pattern) rather than severe or progressive ILD.

The significantly lower mean serum albumin in the ILD deceased group (34.0 g/l versus 39.1 g/l, *p*=0.007) may be as a result of proteinuria from the vasculopathy at a renal level (raised plasma urea may also be related to this). Only 3 participants had SRC but many more likely had proteinuria, which is known to predict mortality in SSc[59]. Another possibility is that a low serum albumin may reflect persistent active inflammation in a more aggressive disease process. In support of this is the trend whereby the baseline median CRP was higher in ILD participants who deceased (9.2 mg/l vs 6.0 mg/l; *p*=0.066), and a higher proportion of participants in the deceased group had a CRP>8 mg/l (66.7% versus 33.3%; *p*=0.065). This is in keeping with findings where CRP>8mg/l was associated with mortality in SSc ILD patients[53, 54]. The limited number of participants unfortunately limited these results, added to which 14.3% participants were missing CRP.

CHAPTER FIVE: CONCLUSIONS AND FUTURE DIRECTIONS

The most important findings from this study are those that are applicable to clinical practice in South Africa. Namely, all of the baseline history and examination features associated with and predictive of SSc ILD are those that a junior doctor could elicit from a patient in a non-specialist clinic. As such, a patient meeting the diagnostic criteria for SSc (particularly dcSSc) who presents with one or more of these features (history of gold-mining, dyspnoea, cough, bibasal crackles), should be referred for investigations of SSc ILD (PFTs and HRCT), and a referral made to a rheumatologist for further, timeous management.

These findings were despite limitations of participant numbers and missing data. The limited number of participants made analysis and application of that analysis difficult, particularly with respect to disease severity, disease progression, disease treatment, and survival. Systemic sclerosis is a rare disease and thus sufficient data will always be a challenge. One way this may be generally improved in order to strengthen the findings of this study is to include data from multiple sites. In this manner other referral centre data could be combined with this data to consolidate current results. Additionally, investigation into why so many patients are lost to follow up should be conducted so that this issue can be addressed. An education programme for patients with group sessions to reinforce information given in doctor consultations, to address compliance problems, and to provide social support may be of benefit.

In terms of data missing from presentation visits, and information missing from follow-up investigations, this may be due to a number of different factors. There is a very busy clinic environment at CHBAH which may lead to information not being documented due to time pressures. One way this may be addressed is to use pro-forma clerking sheets and “tick-box” inserts in patient files to serve as reminders as when to order specific investigations, with regular audit. This would also assist the more junior members of staff who rotate through the department every four months. It would provide additional guidance for them to that already provided from senior staff members in contributing to the overall patient management timeline. To this end, updated patient summaries placed in the front of all patient files may also be helpful. Additionally, pre-filled investigation forms where the patient details alone need to be added may expedite patient visits, or indeed a paperless system would also achieve this, although this would be difficult to initiate and maintain in the current environment. Another factor is equipment failure from blood pressure cuffs, weight scales, laboratory services, to radiology and lung function facilities. Investigation into why this occurs needs to commence, and regular maintenance occur.

Although SSc ILD is a rare disease in the general population, the morbidity and mortality caused to those affected is marked. This study has shown that in this cohort of patients, the diffuse cutaneous disease subtype seems to be the main driver behind the development of ILD, not autoantibodies. Not all dcSSc patients develop ILD and there are some ILD patients that have lcSSc. Anti-centromere antibodies are protective for ILD, and the lack of ACA in Black patients might contribute to the development of ILD in this cohort compared to the international

literature. Contributions from genetic factors remain unelucidated however, and in terms of furthering this body of work, not just consolidating it, this is an important area for future study.

REFERENCES

1. Varga J, Denton CP, Wigley FM, editors. Scleroderma: from pathogenesis to comprehensive management. London: Springer; 2012.

2. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol. 2012 Mar;24(2):165-70.

3. Clements PJ, Furst DE, editors. Systemic Sclerosis. Second ed. London: Lippincott Williams & Wilkins; 2004.

4. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988 Feb;15(2):202-5.

5. Tyndall A, Mueller-Ladner U, Matucci-Cerinic M. Systemic sclerosis in Europe: first report from the EULAR Scleroderma Trials And Research (EUSTAR) group database. Ann Rheum Dis. 2005 Jul;64(7):1107.

6. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA, Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. Arthritis Rheum. 2012 Sep;64(9):2986-94.

7. Tager RE, Tikly M. Clinical and laboratory manifestations of systemic sclerosis (scleroderma) in Black South Africans. Rheumatology (Oxford). 1999 May;38(5):397-400.

8. Illovi CS, Oyoo GO. Characteristics of systemic sclerosis patients in Nairobi, Kenya : a retrospective study. African Journal of Rheumatology. 2013;1(1):23-7.

9. Adelowo OO, Oguntona S. Scleroderma (systemic sclerosis) among Nigerians. Clin Rheumatol. 2009;28(9):1121-5.

10. David M. A case of scleroderma mentioned by Hippocrates in his aphorisms. Korot. 1981;8(1-2):61-3.

11. Fontanetti G. Case of general induration of the skin. Dublin J Med Sci. 1836;13:158-9.

12. Coyle W. A brief history of scleroderma. Scleroderma News. 1988;8(2).

13. Silver RM. Captive of art, not disease. Paul Klee and his illness, scleroderma. Pharos Alpha Omega Alpha Honor Med Soc. 2008 Winter;71(1):16-24.

14. Hensher P. Paul Klee by Philip Hensher. The Guardian. 2011 5 August

15. Klee P. Angel applicant. Heilbrunn Timeline of Art History; 1939.

16. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. Arthritis Rheum. 1996 Aug;39(8):1362-70.

17. Clements PJ, Roth MD, Elashoff R, Tashkin DP, Goldin J, Silver RM, et al. Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis. Ann Rheum Dis. 2007 Dec;66(12):1641-7.

18. Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. Autoimmun Rev. 2011 Mar;10(5):248-55.

19. Mayes MD, Lacey JV, Jr., Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003 Aug;48(8):2246-55.

20. Martin J, Fonseca C. The genetics of scleroderma. Curr Rheumatol Rep. 2011 Feb;13(1):13-20.

21. Gorlova O, Martin JE, Rueda B, Koeleman BP, Ying J, Teruel M, et al. Identification of novel genetic markers associated with clinical phenotypes of systemic sclerosis through a genome-wide association strategy. PLoS Genet. 2011 Jul;7(7):e1002178.

22. Cowie RL, Dansey RD. Features of systemic sclerosis (scleroderma) in South African goldminers. S Afr Med J. 1990 Apr 21;77(8):400-2.

23. Erasmus LD. Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations. S Afr J Lab Clin Med. 1957 Sep;3(3):209-31.

24. Makol A, Reilly MJ, Rosenman KD. Prevalence of connective tissue disease in silicosis (1985-2006)-a report from the state of Michigan surveillance system for silicosis. Am J Ind Med. 2011 Apr;54(4):255-62.

25. McCormic ZD, Khuder SS, Aryal BK, Ames AL, Khuder SA. Occupational silica exposure as a risk factor for scleroderma: a meta-analysis. Int Arch Occup Environ Health. 2010 Oct;83(7):763-9.

26. Chaudhary P, Chen X, Assassi S, Gorlova O, Draeger H, Harper BE, et al. Cigarette smoking is not a risk factor for systemic sclerosis. Arthritis Rheum. 2011 Oct;63(10):3098-102.

27. Solomon DH, Kavanaugh AJ, Schur PH. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheum. 2002 Aug;47(4):434-44.

28. Pudifin DJ, Dinnematin H, Duursma J. Antinuclear antibodies in systemic sclerosis. Clinical and ethnic associations. S Afr Med J. 1991 Nov 2;80(9):438-40.

29. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther. 2003;5(2):80-93.

30. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum. 2005 Aug;35(1):35-42.

31. Champion HC. The heart in scleroderma. Rheum Dis Clin North Am. 2008 Feb;34(1):181-90; viii.

32. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. Eur Respir Rev. 2013 Mar 1;22(127):6-19.

33. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007 Jul;66(7):940-4.

34. Steele R, Hudson M, Lo E, Baron M. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. Arthritis Care Res (Hoboken). 2012 Apr;64(4):519-24.

35. Steen VD, Conte C, Owens GR, Medsger TA, Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum. 1994 Sep;37(9):1283-9.

36. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000 Nov;43(11):2437-44.

37. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum. 2007 Mar 15;57(2):318-26.

38. Gilson M, Zerkak D, Wipff J, Dusser D, Dinh-Xuan AT, Abitbol V, et al. Prognostic factors for lung function in systemic sclerosis: prospective study of 105 cases. Eur Respir J. 2010 Jan;35(1):112-7.

39. Castelino FV, Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. Arthritis Res Ther. 2010;12(4):213.

40. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2012 Aug;71(8):1355-60.

41. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008 Jun 1;177(11):1248-54.

42. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006 Dec;54(12):3962-70.

43. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med. 2007 Nov 15;176(10):1026-34.

44. Matucci-Cerinic M, Steen VD, Furst DE, Seibold JR. Clinical trials in systemic sclerosis: lessons learned and outcomes. Arthritis Res Ther. 2007;9 Suppl 2:S7.

45. Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis Res Ther. 2008;10(5):R124.

46. Dheda K, Lalloo UG, Cassim B, Mody GM. Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. Clin Rheumatol. 2004 Aug;23(4):306-9.

47. Cappelli S, Guiducci S, Bellando Randone S, Matucci Cerinic M. Immunosuppression for interstitial lung disease in systemic sclerosis. Eur Respir Rev. 2013 Sep 1;22(129):236-43.

48. Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of end stage lung disease in a cohort of patients with scleroderma. Ann Rheum Dis. 2003 Feb;62(2):146-50.

49. Plastiras SC, Karadimitrakis SP, Ziakas PD, Vlachoyiannopoulos PG, Moutsopoulos HM, Tzelepis GE. Scleroderma lung: initial forced vital capacity as predictor of pulmonary function decline. Arthritis Rheum. 2006 Aug 15;55(4):598-602.

50. Assassi S, Sharif R, Lasky RE, McNearney TA, Estrada YMRM, Draeger H, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. Arthritis Res Ther. 2010;12(5):R166.

51. Theodore AC, Tseng CH, Li N, Elashoff RM, Tashkin DP. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study. Chest. 2012 Sep;142(3):614-21.

52. Roth MD, Tseng CH, Clements PJ, Furst DE, Tashkin DP, Goldin JG, et al. Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease. Arthritis Rheum. 2011 Sep;63(9):2797-808.

53. Muangchan C, Harding S, Khimdas S, Bonner A, Baron M, Pope J. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research Group. Arthritis Care Res (Hoboken). 2012 Sep;64(9):1405-14.

54. Liu X, Mayes MD, Pedroza C, Draeger HT, Gonzalez EB, Harper BE, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res (Hoboken). 2013 Aug;65(8):1375-80.

55. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980 May;23(5):581-90.

56. Hair JF. Multivariate data analysis: Pearson Prentice HallUpper Saddle, NJ.; 2006.

57. Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. Am Fam Physician. 2008 Oct 15;78(8):961-8.

58. Tangri V HC, Baron M, Bonner A, Fritzler M and Pope J. Associations with Organ Involvement and Autoantibodies in Systemic Sclerosis: Results from the Canadian Scleroderma Research Group (CSRG). Open Journal of Rheumatology and Autoimmune Diseases. [Journal]. 2013;3(2):113-8.

59. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010 Oct;69(10):1809-15.

60. Steen VD, Owens GR, Redmond C, Rodnan GP, Medsger TA, Jr. The effect of D-penicillamine on pulmonary findings in systemic sclerosis. Arthritis Rheum. 1985 Aug;28(8):882-8.

61. de Clerck LS, Dequeker J, Francx L, Demedts M. D-penicillamine therapy and interstitial lung disease in scleroderma. A long-term followup study. Arthritis Rheum. 1987 Jun;30(6):643-50.

62. Derk CT, Huaman G, Jimenez SA. A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. Br J Dermatol. 2008 May;158(5):1063-8.

APPENDIX A: Preliminary classification criteria for systemic sclerosis[55]

One major criterion or two minor criteria.

Major Criterion:

- Proximal scleroderma

Minor Criteria:

- Sclerodactyly
- Digital pitting, or scars, or loss of substance from finger pad
- Bibasilar pulmonary fibrosis

APPENDIX B: Data collection sheet

Participant study number: _____ Date of 1st visit:_____

Date of last visit: _____

Demographics

Age: _____

Gender:

M	F

Ethnicity:

B	W	C	I	O

	YES	NO	DETAILS
Mining exposure			
Toxin exposure			
Current occupation			

	Yes	No		Number/day	Years	Years stopped
Smoker			If yes			
Ex-smoker			If yes			

Date of onset of first non-Raynaud's symptom: _____

Disease duration: _____

Age at onset: _____

Age at diagnosis:_____

History

	YES	NO	DATE OF ONSET	DETAILS
Raynaud's				
Reflux/Dysphagia				
Myalgia/weakness				
Arthritis/arthralgia				
Dyspnoea				NYHA class:
Cough				
Tightening of skin on hands/face				

Other medical History:

	Yes	No	Date of onset	Details
HIV				
TB				

Examination

ACR criteria fulfilled: Y N

Disease subset: Diffuse | Limited | Unclassified

Weight: _____ kg

Pulse rate: _____ /min regular/ irregular

Blood pressure: ____ /_____

Maximum modified Rodnan Skin score: _____

	YES	NO	DETAILS
Sclerodema			
Digital scars			
Digital ulcers active			
Digital gangrene			
Nailfold changes			
Telangiectasia			
Calcinosis			
Arthritis			
Tendon friction rubs			
Proximal Myopathy			
SRC			

Breath sounds:

	Yes	No
Normal		
Crackles – basal		
Crackles – Diffuse		
Wheezes		

Clubbing: Y N

Requires oxygen: Y N

Investigations

Urinalysis:

	Yes	No
Dipstix 1+ protein		
Dipstix 2+ protein		
Dipstix 3+ protein		
Urine PCR		

ECG:

	YES	NO	DETAILS
Arrythmias			
Conduction block			

Echo:

	YES	NO	
Pulmonary hypertension			If yes, PAPsys =
Pericardial effusion			
LVEF% =			

ILD:

Y	N

Date ILD diagnosis:			
	YES	NO	Date
Velcro crackles			
CXR fibrosis			
HRCT			
PFT			

CXR:

	Yes	No	Date
Normal			
Fibrosis			

HRCT: (at diagnosis)

	Yes	No
Normal		
Ground glass		
Honeycombing		
Fibrosis		
PAH		

PFT at diagnosis:

TLC (% pred)	
FEV1 (% pred)	
FVC (% pred)	
DLCO (% pred)	

	YES	NO
Restrictive		
FVC > 70%		
FVC 50 – 69%		
FVC < 50%		

Barium swallow:

Date			
	YES	NO	Details
Oesophageal reflux			
Oesophageal dysmotility			

Laboratory:

ANA titre		CRP	
Centromere		ESR	
Speckled		C3	
Nucleolar		C4	
Homogenous		Hb	
Ds DNA		MCV	
Sm		HCT	
Ro		WCC	
La		Neuts	
RNP		Lymphs	
RF		Eos	
Scl-70		Na	
Lupus anticoagulant		K	
IgM anticardiolipin		urea	
IgG anticardiolipin		creat	
TChol		CK	
LDH		alb	

Treatment

	Route	Dose	Start date	Stop date	Details
Steroids		mg/d			
Cyclophos		mg/4 wks			
Methotrexate		mg/wk			
Azathioprine		mg/d			
MMF		mg/d			
Iloprost					
PPI					
Nifedipine					
ACE-i/ARB					
Statin					
Aspirin					

POST TREATMENT FOLLOW-UP PFT

	6 months	12 months	24 months
TLC			
FEV1			
FVC			
FEV1/FVC			
DLCO			

SURVIVAL DATA

	YES	NO	DATE
DECEASED			
ALIVE			
LOST TO FOLLOW UP			

	YES	NO
Infection		
Malignancy		
ILD		
CVS		
Renal		
Other		

APPENDIX C: Ethical Approval Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Phillipa Ashmore

CLEARANCE CERTIFICATE	M120966
PROJECT	Interstitial Lung Disease in South Africans with Systemic Sclerosis
INVESTIGATORS	Dr Phillipa Ashmore.
DEPARTMENT	Department of Internal Medicine
DATE CONSIDERED	28/09/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/09/2012 CHAIRPERSON ..... (Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof M Tikly

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.