Clinical profile of scleroderma associated interstitial lung disease at a tertiary hospital in KwaZulu-Natal, South Africa: A retrospective 7 years review.

By

Salah Tanish

Submitted in partial fulfillment of the academic requirements for the degree of MMed

In the Department of Internal Medicine

School of Clinical Medicine College of

Health Sciences University of

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Durban

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As the candidate's supervisors I have approved this thesis for submission.

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Declaration

I Salah Tanish declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

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Abstract

Background:

Interstitial lung disease (ILD) is one of the most serious complications among patients with scleroderma. It is associated with significant morbidity and mortality. Little is known about the epidemiology of scleroderma-associated interstitial lung disease in sub-Saharan Africa. Thus, we aimed to determine the prevalence, clinical characteristics and outcomes of patients with scleroderma-ILD.

Methods:

A retrospective electronic chart review was conducted of patients with systemic sclerosis seen between January 2010 and December 2016 in the Departments of Pulmonology and Rheumatology at Inkosi Albert Luthuli Central Hospital, Durban, South Africa.

Results:

A total of 146 patients with systemic sclerosis (SSc) were seen during the study period. Fifty-five patients had systemic sclerosis-associated ILD, giving a prevalence of 37.7%. The median age was 51 (IQR 41-60) years, 87% of patients were female and 56% were of Indian descent. Dyspnoea was the presenting complaint in 47 (85.4%) patients, while 16 (29.1%) presented with cough. Antinuclear factor (ANA) was positive in 50 patients (90.9%), anti-Scl-70 antibodies were positive in 21 (38.2%). Thirty-seven patients (67.3%) received immunosuppressants, with 27 (49.1%) receiving cyclophosphamide as induction therapy, while 18 (32.7%) patients did not receive any specific therapy. Most patient symptoms remained static during the period of observation. Usual interstitial pneumonia (UIP) pattern was the most common radiological diagnosis. Follow-up computer tomography (CT) scans were available in 48 (87%) patients, with the majority of patients showing no significant radiological changes between their first and last CT scans. Follow-up lung function testing showed a statistically significant decrease in median forced vital capacity (FVC) of 0.09l (p=0.011). Overall 20 (36.4%) patients had a significant decline in FVC, while 7 (12.7%) had an improvement in FVC.

Conclusion:

ILD is common in systemic sclerosis, affecting 1 in 3 patients with systemic sclerosis in this cohort. Immunosuppressant treatment may arrest or retard the rate of decline in lung function.

Table of Contents

List of Abbreviations

	Abbreviation	Full text
1	SSc	Systemic sclerosis
2	ILD	Interstitial lung disease
3	SSc-ILD	Systemic sclerosis associated interstitial lung disease
4	PAH	Pulmonary arterial hypertension
5	CXR	Chest X ray
6	CRP	C-reactive protein
7	ESR	Erythrocyte sedimentation rate
8	HRCT	High-resolution computed tomography
9	NSIP	Nonspecific interstitial pneumonitis
10	UIP	Usual interstitial pneumonia
11	BOOP	Bronchiolitis obliterans organizing pneumonia
12	PFTs	Pulmonary function tests
13	FVC	Forced vital capacity
14	FEV 1	Forced expiratory volume in 1 second
15	TLC	Total lung capacity
16	VC	Vital capacity
17	DLCO	Diffusion capacity of carbon monoxide
18	BAL	Broncho- alveolar lavage
19	ANAs	Antinuclear antibodies
20	Scl-70	Anti-Scleroderma-70
21	ACA	Anti-centromere antibody
22	PDGF	Platelet- derived growth factor
23	MMF	Mycophenolate mofetil
24	AZA	Azathioprine
25	CYC	Cyclophosphamide
26	IQR	Interquartile range
27	RA	- Rheumatoid arthritis
28	SLE	Systemic lupus erythematosus
29	HIV	Human immune deficiency virus

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Part 1

Chapter One

Introduction:

Systemic sclerosis (SSc) is a multisystem disease characterized by inflammation and fibrosis of multiple organs. It is an autoimmune systemic disorder characterized by immune dysregulation, extracellular matrix production and small vessel vasculopathy. The fibroblast dysfunction results in fibrosis of the internal organs and skin, along with the production of autoantibodies (1).

There are two major subtypes, limited cutaneous scleroderma (previously known as CREST syndrome) and diffuse cutaneous scleroderma(dcSS). The main difference is the extent of skin involvement and visceral involvement. Limited scleroderma patients often have a long history of Raynaud's phenomenon before development of other symptoms. They have skin thickening limited to hands, and distal to elbows, and frequently have problems with digital ulcers and oesophageal dysmotility. Although generally a milder form than diffuse scleroderma, they can develop life-threatening complications from small intestine hypomotility as well as pulmonary hypertension (2).

Pulmonary involvement is a common complication in patients with SSc and most often comprises fibrosis or interstitial lung disease (ILD), and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH). Using pulmonary function tests, significant pulmonary involvement is detectable in 25% of the patients with SSc within 3 years from initial diagnosis (3). To differentiate between ILD, PAH and other causes of dyspnoea in patients with SSc can be clinically challenging. Respiratory symptoms can be non-specific, and early-stage pulmonary fibrosis can progress undetected. On clinical examination, crackles may be subtle in early disease; and thus may be missed entirely. The examiner has to listen very carefully, particularly at the bases and laterally. The chest radiograph may show small volume lungs. Increased peripheral markings at bases and peripherally and a shaggy heart border are early features of ILD. However, the identification and staging of pulmonary manifestations is of paramount

importance in the management of these patients. Respiratory manifestations are the leading cause of disease-related mortality and morbidity in patients with SSc. A recent report estimated the mortality from respiratory disease in SSc patients, in the presence or absence of cardiac disease, to be 33% (4).

Literature Review

Interstitial lung disease:

ILD is one of the most common complications in scleroderma. In early autopsy studies up to 100% of patients were found to have parenchymal involvement (5). On high-resolution computed tomography (HRCT) about 90% of patients will have interstitial abnormalities (6), and as many as 40–75% will have changes in pulmonary function tests (PFTs) (7). Parenchymal lung involvement often appears early after the diagnosis of SSc, with 25% of patients developing clinically significant lung disease within 3 years as defined by physiological, radiographic or bronchoalveolar lavage (BAL) abnormalities (8). Risk factors for SSc-ILD are African–American ethnicity, skin score, creatine phosphokinase levels and serum creatinine, cardiac involvement and hypothyroidism. Genetic factors and specific serological findings play a role. Anti-endothelial cell and anti-topoisomerase antibodies predict the presence of lung involvement, and anti-centromere and anti-RNA polymerase III antibodies are less associated with lung disease. Patients with diffuse systemic sclerosis (dcSSc) have a higher incidence of interstitial lung disease (9).

Epidemiology:

SSc-ILD is not a common disease. It has an incidence of 10–50 cases per million people per year, a prevalence of 40–340 cases per million people, and substantial geographic variability (10). Interstitial findings of the disease are evident on high-resolution CT (HRCT) of the chest in up to 80% of patients with SSc. The prevalence of ILD increases during the course of the disease. Early development of SSc-ILD (ie, less than 3 years after diagnosis) is increasingly seen

and could be associated with poor outcomes (11).

Male sex, African American race, and diffuse skin disease are demographic factors associated with the presence of systematic sclerosis-associated ILD. SSc-ILD is also more common among patients with nail fold capillary abnormalities, digital ulcers, longer disease duration, and pulmonary hypertension on screening echocardiogram (12). SSc-ILD is known to be more common among patients who have anti-topoisomerase antibodies than in patients without, and it is relatively rare among people with anti-centromere antibodies (13).

In addition to autoantibodies, researchers are increasingly interested in the role of molecular markers as predictors of SSc-ILD. These include cytokines (eg, interleukin-6 [IL-6] and IL-34), chemokines (eg, CXCL4 and CCL18), enzymes (eg, chitinase-1 and lysyl oxidase), matrix proteins (eg, tenascin-C and cartilage oligomeric matrix protein), inflammatory proteins (eg, serum amyloid A), and pneumocyte products (eg, surfactant protein D, carbohydrate antigen 15-3 and Krebs von den Lungen-6 [KL-6]) (13).

Pathogenesis:

SSc-ILD is thought to be the result of the interplay between multiple factors such as autoimmunity, fibrosis, inflammation, and vascular injury. The initial event has been proposed to be an injury to the alveolar epithelium or vasculature, followed by aberrant activation of the immune system, which promotes fibroblast recruitment and activation, extracellular matrix overproduction, and eventually the replacement of normal pulmonary architecture by fibrous tissue (14).

The presence of lung injury is suggested by the detection of high serum concentrations of alveolar epithelial cell products such as surfactant protein D and KL-6 in patients with SSc-ILD (14).

This injury is believed to result in the release of profibrotic stimuli that induce the differentiation of fibroblasts to myofibroblasts, with the participation of coagulation factors, cytokines, growth factors, and inflammatory cells. The process of epithelial-mesenchymal transition, through which epithelial cells lose their polarity and acquire mesenchymal properties, has been proposed to be a key mechanism mediating the transition from injury to inflammation and fibrosis (15).

The current literature supports this hypothesis, identifying a number of functional autoantibodies as potential culprits for the vascular injury. Stimulatory antibodies targeting the platelet derived growth factor receptor have been reported in the serum of patients with SSc and could potentially have a role in the fibrosing process. Anti-endothelial antibodies have been detected in the circulation of patients with SSc and have been shown to induce both endothelial cell activation and apoptosis (16).

Diagnosis:

The early identification and treatment of ILD may prevent deterioration of lung function. The best way for diagnosing early disease is screening for ILD in scleroderma patients. Early ILD is usually asymptomatic. The most common symptoms are fatigue, exertional dyspnoea initially, and dry cough. Chest pain is infrequent and heamoptysis is rare (17).

The most characteristic finding of ILD is bilateral fine inspiratory crackles (i.e., "Velcro" rales) on physical examination of the lung bases (18). The presence of anti-topoisomerase I/Scl-70, anti-U3RNP, Th/To, and antihistone autoantibodies at presentation may identify those SSc patients who are at high risk for ILD (19).

However, the presence of anti-topoisomerase/Scl-70 has limited sensitivity for SSc-related ILD. Patients with SSc-associated ILD are frequently found to have abnormal pulmonary function tests, including those who have mild or absent respiratory symptoms and normal chest radiographs. However, early ILD cannot be excluded by normal spirometry. The earliest detectable functional correlate of lung disease in SSc is a reduction in diffusion capacity of carbon monoxide (DLCO). This is present in over 70% of patients. The decrease in DLCO correlates with the severity of ILD detected by HRCT and is a predictor of poor outcome. It is also a risk factor for pulmonary hypertension (20).

Whereas the chest radiograph seems relatively insensitive for the detection of early ILD, the use of HRCT appears much more sensitive. The earliest HRCT change of ILD is usually ill-defined, subpleural crescents of increased density in the posterior segments of both lower lobes. With progressive disease, the shadowing takes on a ground-glass pattern and reticular appearance and may be associated with fine honeycomb air spaces, and traction bronchiectasis (20, 21).

The extent of pulmonary fibrosis seen on HRCT is negatively correlated with forced vital

capacity (FVC) and is a powerful predictor of survival. It is important to perform HRCT in the prone as well as supine positions, particularly in patients with subtle findings. This will help eliminate radiographic changes resulting from gravity-induced vascular and interstitial pooling in dependent areas of the lung (17).

Histological finding:

Since SSc-associated ILD is predominantly sub-pleural, significant histological changes are more likely to be found in peripheral lung biopsy than from tissue sampling of other locations. While lung biopsy guided with thoracoscopy is seldom warranted in SSc, it may be indicated in the evaluation of patients with lung findings suggestive of other disease processes (22).The most noted histopathologic finding on lung biopsy in SSc is nonspecific interstitial pneumonitis (NSIP) (23).

The HRCT appearance may correlate with lung biopsy findings. An isolated ground-glass pattern of opacification on HRCT is usually associated with a biopsy showing predominantly cellular infiltration or NSIP (20) .

The presence of ground-glass opacification correlates with increased numbers of inflammatory cells in the bronchoalveolar lavage (BAL) fluid. In comparison, a reticular HRCT pattern is generally associated with a primarily fibrotic histologic picture, consistent with usual interstitial pneumonia (UIP), on lung biopsy (20).

The severity of lung involvement (defined by HRCT) may correlate with the type of inflammatory cells obtained by BAL from the affected areas: excess lymphocytes may be present despite a normal appearance; excess eosinophils are associated with early, less extensive disease, and neutrophils are associated with more extensive disease (24).

Patients with scleroderma-ILD typically have elevated numbers of granulocytes in their BAL fluid, particularly neutrophils and eosinophils and lymphocytes. Some centres perform BAL at presentation in SSc patients with evidence of lung disease (25)

Management:

The potential benefit of treatment must be weighed against the risks of therapy on a case-by-case

basis. Unfortunately, whether to initiate therapy or not can be a difficult decision because the benefits of therapy appear to be modest, and the toxicities can be significant. That is the reason for some clinicians suggesting that immunosuppressive therapy should be initiated in patients with SSc-associated ILD who have respiratory symptoms, abnormal and/or declining pulmonary function, evidence of progressive (i.e., active) disease, and with no contraindications to therapy. The features of active disease may include an early disease stage, abnormal and/or declining pulmonary function, and possibly, ground-glass opacity on HRCT. Immunosuppressive therapy is the main stay of the treatment of SSc-related ILD. Other important aspects of management include: avoiding or stopping tobacco use, vaccinations against influenza, pneumococcus, covid-19, and use of proton pump inhibitors, and pulmonary rehabilitation (17).

In response to multiple uncontrolled case series that reported clinical, spirometric, DLCO, and radiographic improvements in SSc-ILD patients treated with oral or intravenous cyclophosphamide, two major prospective studies were recently performed. In a first double-blind multicenter trial (the Scleroderma Lung Study), 158 patients with early SSc-associated ILD, dyspnoea, and evidence of active alveolar inflammation were randomly assigned to receive either oral cyclophosphamide (≤2 mg/kg) or placebo daily for 1 year (26). These results indicate that a 1-year course of oral daily cyclophosphamide has significant, albeit modest, clinical efficacy for the treatment of patients with early SSc and active symptomatic alveolitis. However, the toxicity of daily oral cyclophosphamide is significant, and the decision to initiate therapy must carefully balance risk versus potential benefit. A follow-up study reported 24-month outcomes for 93 of the 109 patients who completed 1 year of oral cyclophosphamide or placebo. Of the 48 patients who had received cyclophosphamide, 12 also received low-dose prednisone. The beneficial effects of cyclophosphamide on FVC appeared to persist for 6 months after stopping the drug (27). However, by 24 months, the improvement in FVC was no longer present, suggesting that the response to cyclophosphamide is not durable and that a maintenance regimen should be considered. Improvement in respiratory symptoms, as well as in skin induration, persisted in the cyclophosphamide-treated group at 24 months. In the second prospective trial, 45 patients were randomly assigned to receive six-monthly intravenous infusions of cyclophosphamide plus prednisolone (20 mg on alternate days) (28). At 12 months, there was a modest improvement of FVC in the cyclophosphamide group after, adjustment for baseline FVC, but this improvement did not achieve statistical significance in this small study. Neither DLCO nor measures of dyspnoea showed improvement in either group.

In a meta-analysis, Nannini et al. concluded that cyclophosphamide treatment in patients with systemic sclerosis-related ILD did not result in clinically significant improvement of pulmonary function. In these two randomized studies, both patients with stable and worsening ILD were likely to have been included. Silver et al. first treated patients with worsening ILD, i.e., a significant decline of lung volumes and/or DLCO before initiating cyclophosphamide. They showed that a majority of patients stabilized with cyclophosphamide (29).

In studies evaluating the efficacy of cyclophosphamide versus placebo in SSc-associated ILD, many patients have also received low-dose glucocorticoids. For this reason and because of the attendant risk of SSc renal crisis, a low-dose glucocorticoid (equivalent of ≤ 10 mg per day of prednisone) is usually recommended with cyclophosphamide (28).

Azathioprine appears less efficacious in SSc-associated ILD than oral daily cyclophosphamide. In an unblinded trial (30). 60 patients with early diffuse SSc and ILD were randomly assigned to receive either cyclophosphamide (up to 2 mg/kg per day) or azathioprine (2.5 mg/kg per day). During the first 6 months of therapy, patients in both groups also received prednisolone (15 mg/day), which was subsequently tapered. After 18 months, FVC and DLCO were stable in patients treated with cyclophosphamide but had declined in patients treated with azathioprine. Leukopenia was more frequent in the cyclophosphamide group. Preliminary data suggest that azathioprine may have a role as maintenance therapy in patients who have completed a course of cyclophosphamide. A retrospective series of 20 patients with SSc-associated ILD found stabilization or improvement in pulmonary function tests after a combination of 6 months of monthly intravenous cyclophosphamide followed by 18 months of azathioprine.

Mycophenolate mofetil (MMF) is an inhibitor of lymphocyte proliferation that may prove to be safe and effective for the treatment of SSc-associated ILD (31). The findings from SLS II (32) are consistent with the evidence from previous studies showing the efficacy of both cyclophosphamide and MMF in improving lung function in patients with progressive SSc-ILD. In addition to that, MMF was shown to be less toxic and better tolerated than cyclophosphamide, with significantly fewer withdrawals from the study drug. Concurrent improvements in skin scores suggest an overall systemic benefit and improvements in dyspnoea. Taken in consideration, all these findings support the increasingly common practice of prescribing MMF for patients with SSc-ILD.

Immunoablative therapy followed by autologous hematopoietic stem cell infusion has been used in some patients with severe SSc, with a stabilization of lung volumes (33).

Imatinib mesylate, an inhibitor of PDGF, c-kit, and c-abl protein tyrosine kinase, is highly effective for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors. Whether imatinib mesylate or other tyrosine kinase inhibitors may be helpful in SSc patients with ILD remains currently unknown (34).

Lung transplantation is an option for patients with SSc-associated severe ILD that is not responsive to pharmacologic interventions. Carefully selected SSc patients undergoing lung transplantation have similar morbidity and mortality than patients undergoing lung transplantation for idiopathic pulmonary fibrosis. This was illustrated in a retrospective review of the result of lung transplantation in nine patients with SSc-associated ILD (35).

Prognosis:

In patients with SSc, the presence of ILD predicts increased mortality. The most rapid decline in FVC occurs within the initial 3 years of disease onset, indicating that lung injury and fibrosis are early complications.

The prognostic value of lung biopsy in patients with SSc-associated ILD is limited. Clinical severity and lung function impairment are indeed better predictors of outcome than histopathologic subtypes.

In a retrospective histopathological evaluation of 80 patients with SSc and biopsy-proven ILD, 76% had NSIP and 11% had UIP. The 5-year survival rate for patients with NSIP and UIP was slightly better for NSIP (36).

Markers of a worse prognosis included a lower DLCO and a more rapid decline of DLCO over 3 years.

The prognostic value of BAL is uncertain. One retrospective study reported that increased eosinophils in the BAL fluid was associated with a poorer prognosis (37).

An increased proportion of neutrophils in BAL fluid was associated with more extensive lung disease on HRCT, a greater reduction in DLCO, and early mortality but it did not predict the rate of functional deterioration or progression-free survival (38).

Research Question and Hypothesis:

What is the research question or the hypothesis?

Scleroderma associated interstitial lung disease frequency, spectrum of disease radiological features and clinical outcomes in Kwa Zulu Natal South Africa are similar to what has been described in the international data.

The aim of this study?

To determine the patient profile and treatment outcomes of patients that develop scleroderma associated interstitial lung disease in the South African context.

The objectives of the study:

a. To determine the prevalence of patients that develop interstitial lung disease in scleroderma.
b. To describe the demographic profile of the study participants.
c. To examine the specific patterns of interstitial lung disease on HRCT scan.
d. To examine the management options that patients were placed on for interstitial lung disease and treatment specific outcomes.
e. To assess the positive anti-scleroderma antibodies and anticentromere antibodies and hdevelopment of interstitial lung disease.
f. To assess pulmonary function test (PFT) parameters before and after treatment.
g. To assess chest radiograph finding of patients with interstitial lung disease.
h. To determine if there is any increased risk with HIV.

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Part 2: A submission ready manuscript.

Prevalence and outcomes of systemic sclerosis-associated interstitial lung disease at a tertiary level hospital in KwaZul -Natal, South Africa: a retrospective review.

Salah Tanish
Kennedy Nyamande
K de Vasconcellos

Abstract

Background:

Interstitial lung disease (ILD) is one of the most serious complications among patients with scleroderma. It is associated with significant morbidity and mortality. Little is known about the epidemiology of scleroderma associated ILD in sub-Saharan Africa. Thus, the aim was to determine the prevalence, clinical characteristics and outcomes of patients with scleroderma-ILD.

Methods:

A retrospective electronic chart review was conducted of patients with systemic sclerosis seen between January 2010 and December 2016 in the Departments of Pulmonology and Rheumatology at Inkosi Albert Luthuli Central Hospital, Durban, South Africa.

Results:

A total of 146 patients with systemic sclerosis (SSc) were seen during the study period. Fifty-five had SSc-associated ILD, giving a prevalence of 37.7%. The median age was 51 (IQR 41-60) years, 87% of patients were female and 56% were of Indian descent. Dyspnoea was the presenting complaint in 47 (85.4%) patients, while 16 (29.1%) presented with cough. Antinuclear factor (ANA) was positive in 50 patients (90.9%), anti-Scl-70 antibodies were positive in 21 (38.2%). Thirty-seven patients (67.3%) received immunosuppressants, with 27 (49.1%) receiving cyclophosphamide as induction therapy, while 18 (32.7%) patients did not receive any specific therapy. Most patient symptoms remained static during the period of

observation. UIP was the most common radiological diagnosis. Follow-up CT scans were available in 48 (87%) patients, with the majority of patients showing no significant radiological changes between their first and last CT scans. Follow-up lung function testing showed a statistically significant decrease in median FVC of 0.09l (p=0.011). Overall 20 (36.4%) patients had a significant decline in FVC, while 7 (12.7%) had an improvement in FVC.

Conclusion:

ILD is common in systemic sclerosis, affecting 1 in 3 patients with systemic sclerosis in our cohort. Immunosuppressant treatment may arrest or retard the rate of decline of lung function.

Keywords:

Scleroderma –interstitial lung disease –KwaZulu-Natal-South Africa

Introduction:

Systemic sclerosis (SSc) is a systemic autoimmune disorder characterised by excessive extracellular matrix production, due to a small vessel vasculopathy coupled with immune dysregulation. The production of autoantibodies causes fibroblast dysfunction and results in fibrosis of the skin and internal organs (1). The pathogenesis of SSc remains unclear, even though recent research has focused on a variety of pathways that might lead to new therapeutic targets (2).

Pulmonary involvement is common in patients with SSc and most often comprises fibrosis or interstitial lung disease (ILD), and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH). Using pulmonary function tests (PFTs), significant pulmonary involvement is detectable in 25% of patients with SSc within 3 years of initial diagnosis (3). Pulmonary manifestations are the leading cause of disease-related morbidity and mortality in patients with SSc. A recent report estimated the mortality from pulmonary disease in SSc patients to be 33 % (4). Interstitial lung disease is more common among African Americans and in people with the diffuse cutaneous form of systemic sclerosis or anti-topoisomerase 1 antibodies. Systemic sclerosis-associated ILD most commonly presents with dyspnoea, cough,

and a non-specific interstitial pneumonia pattern on high resolution computed tomography (HRCT), with a minority of cases fulfilling the criteria for usual interstitial pneumonia.

The standard therapy has traditionally been combinations of immunosuppressants, particularly mycophenolate mofetil or cyclophosphamide (5, 6). Glucocorticoids are still frequently used but have shown limited benefit and may increase risk of scleroderma renal crises (10,12). Although definitive data are lacking, mycophenolate mofetil (MMF) appears to improve patient outcome in SSc-ILD with a reasonable safety profile, and may be considered as first line therapy in these patients (7-11). Azathioprine (AZA) has not been well investigated but appears to be a well-tolerated agent for maintenance therapy in patient with SSc-ILD (7, 12, 13). There is limited data available on scleroderma-associated interstitial lung disease in Southern Africa. A retrospective review of SSc patients attending a tertiary connective tissue diseases clinic compared patients with and without ILD (14).

Given the probable role of genetic and/or environmental factors in the pathogenesis of this disease, and in the response to therapy, it is important to evaluate differences in geographic regions and patient populations. The aims of the study were: a) to determine the patient profile and b) outcomes of patients with scleroderma-associated interstitial lung disease in Durban, KwaZulu-Natal, South Africa.

Materials and Methods:

This study was a retrospective observational descriptive study using data obtained from preexisting electronic patient records. It was conducted at Inkosi Albert Luthuli Central Hospital, an 800-bedded central referral hospital in Durban, KwaZulu-Natal South Africa. The study included all adult patients (18 years and older) diagnosed with scleroderma with interstitial lung disease who were seen in the pulmonology clinic between 01/01/2010 and 31/12/2016. The clinic is a referral clinic accepting patients throughout the province of KwaZulu-Natal. The study excluded patients where electronic data sets could not be retrieved due to technical issues, those younger than 18 years and patients with other connective tissue diseases.

Demographic and clinical data, as well as data from special investigations, were captured retrospectively from medical records. Demographic data included age, gender and race. Clinical data captured were presenting symptoms, pre-existing medical conditions, functional class, date of onset of initial symptoms, and treatment. Special investigations captured

included results of HRCT, antinuclear factor (ANA), anti-Scleroderma-70 (Scl-70), and anti-centromere antibody (ACA) levels, and PFT. There is no valid definition of SSc-ILD disease progression, but we defined a decline of ≥ 10% in any pulmonary function parameter as being significant deterioration, with an increase of at least ≥10% from base line as being significant improvement.

Ethical approval was granted by the University of KwaZulu-Natal's Human Research Ethics Committee (ref. no. BE602/18) and the KwaZulu-Natal department of Health (ref. no. KZ_201905_016).

Statistical analysis was performed using SPSS version 27. Basic descriptive statistics were performed with continuous variables expressed as median and interquartile range (IQR) and categorical variables expressed as number and proportions. Categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. The related-samples Wilcoxon signed-rank test was used to compare first and last pulmonary function test results. A p-value of <0.05 was deemed statistically significant.

Results:

A total of 146 patients with systemic sclerosis were seen during the study period. Fifty-five of these patients had SSc-associated ILD. The prevalence of ILD in systemic sclerosis was 37.7%.

In the patients with SSc-ILD, the median age was 51 years (IQR 41-60). Forty-eight (87.3%) were female and 31 (56.4%) were Asian with 22 (40%) being black Africans. Forty-one had other co-morbidities, including overlap with other connective tissue diseases (see Table 1). Eighteen (32.7%) patients had pulmonary hypertension, the median pulmonary arterial pressure on echocardiography was 43 mm Hg (IQR 40-60) and the maximum recorded PAP was 100 mm Hg Four (7.3%) patients had osteoporosis. Three patients were HIV positive. All 3 were on antiretroviral therapy and their CD4 counts ranged from 568 to 630 cells/ul

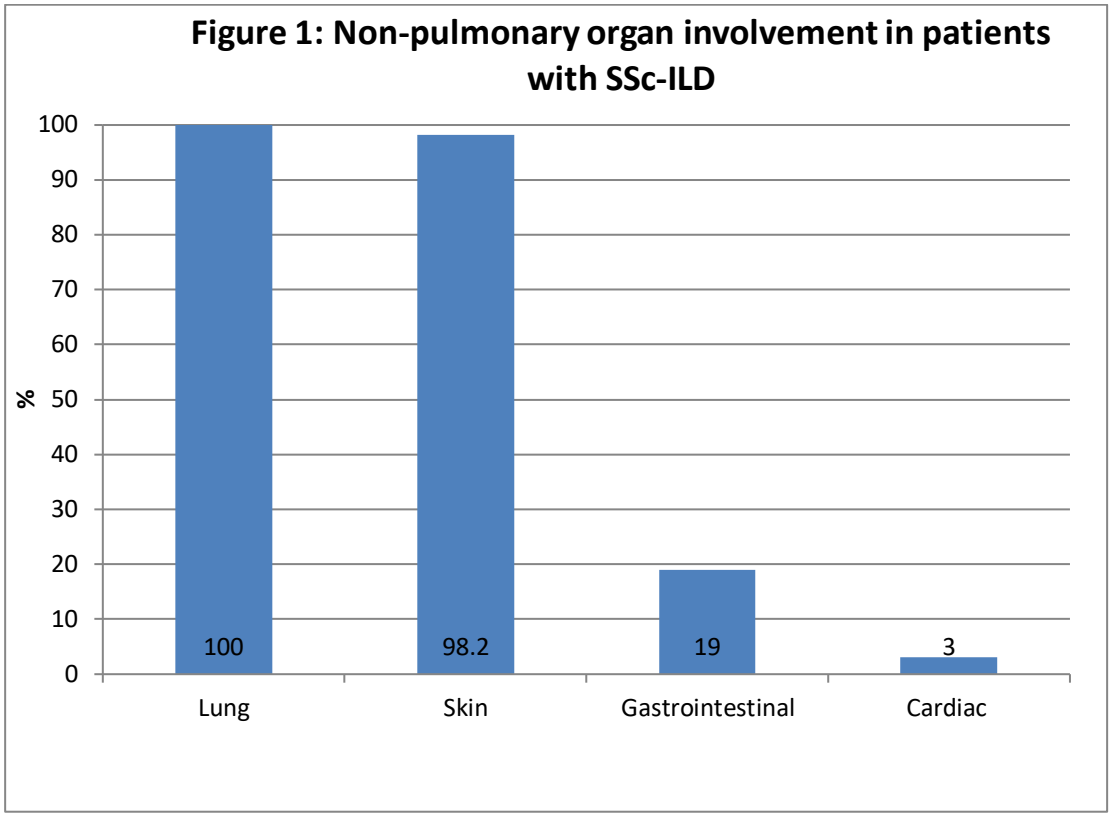
Table 1: Baseline demographic data

		n (%) or median (IQR)
Age (years)		51 (41-60)
Gender	Female	48 (87.3%)
	Male	7 (12.7%)

Race	Asian	31 (56.4%)
	Black	22 (40%)
	Coloured	2 (3,6%)
HIV status	Negative	52 (94.5%)
	Positive	3 (5.5%)
Associated rheumatological conditions	SLE	10 (18.2%)
	Polymyositis/dermatomyositis	5 (9,1%)
	RA	3 (5,5%)
	Sjogren syndrome	1 (1.8%)

Details of patients' presenting symptoms are shown in Table 2 and a summary of non-pulmonary organ involvement is shown in Figure 1.

Table 2: presenting symptoms		
		n (%)
Skin tightness		49 (89.1%)
Dyspnea		47 (85.4%)
Raynaud's phenomena		46 (83.6%)
Dysphagia		23 (41.8%)
Cough		16 (29.1%)
Dyspnea grade	1	7 (12.7%)
	2	32 (58.2%)
	3	7 (12.7%)
	4	1 (1.8%)

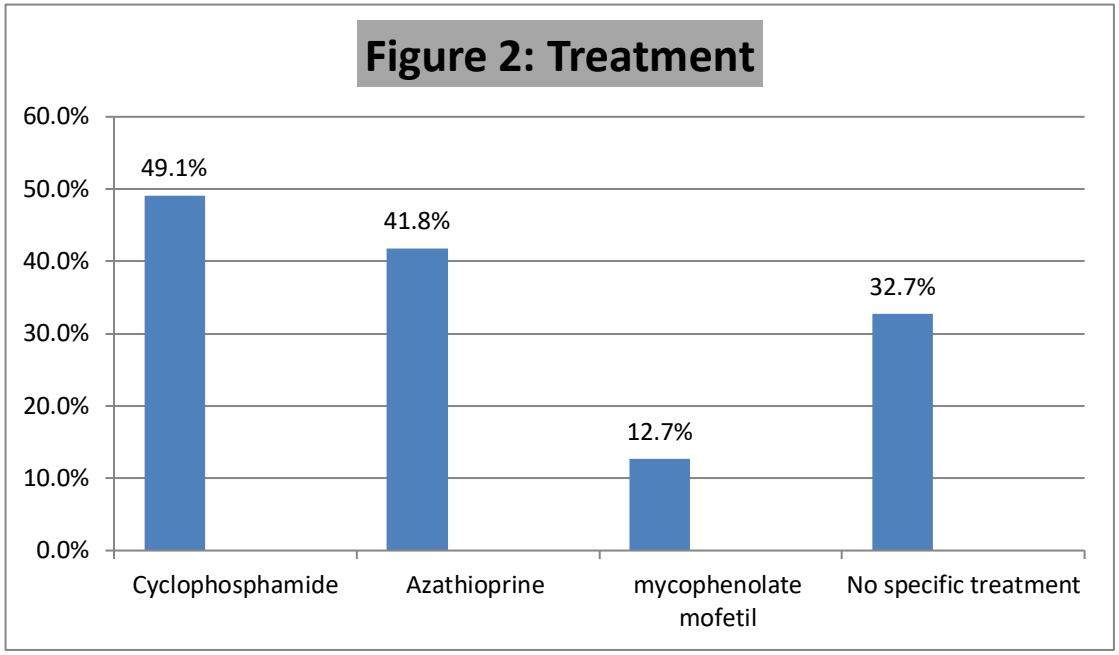


The results of serological testing are shown in Table 3. The median ANA titre was 800 (IQR 200-2560), with the median anti-Scl-70 titre being 141 (IQR 38-320) anti-centromere antibodies were only positive in one patient, who had a titer of 240 KAU.

Table 3: results of serological testing

		n (%)
ANA	Negative	4 (7.3%)
	Not available	1 (1.8%)
	Positive	50 (90.9%)
Anti-centromere antibodies	Negative	13 (23.6%)
	Nont available	41 (74.5%)
	Positive	1 (1.8%)
Anti-Scl-70 antibodies	Negative	24 (43.6%)
	Nont available	10 (18.2%)
	Positive	21 (38.2%)

A total of 37 patients (67.3%) received immunosuppressants. The individual agents received are shown in Figure 2. Of note patients may have received more than one immunosuppressant during their follow up.



Symptom progress over the follow-up period from the time of diagnosis is shown in Table 4

Table 4: symptom progress

		n (%)
General symptoms		
Skin tightness	Improved	3 (5.5%)
	Static	43 (78.2%)
	Worsened	9 (16.4%)
Raynaud's phenomenon	Improved	2 (3.6%)
	Static	50 (90.9%)
	Worsened	2 (3.6%)
Dysphagia	Improved	2 (3.6%)
	Static	47 (85.5%)
	Worsened	6 (10.9%)
Respiratory symptoms		

Dyspnea	Improved	11 (20%)
	Static	36 (65.5%)
	Worsened	7 (13.0%)
Cough	Improved	3 (5.5%)
	Static	47 (85.5%)
	Worsened	5 (9.1%)

Follow-up CT scans were available in 48 (87%) patients, with the majority of patients showing no significant radiological changes between their first and last CT scans. UIP was the most common radiological diagnosis, being found in 24 (43.6%) patients. Other findings on HRCT included bronchiectatic changes, ground glass appearance and fibrosis. The HRCT findings for the cohort are shown in table 5.

Table 5: CT findings		
		n (%)
Initial HRCT findings	NSIP	9 (16.4%)
	UIP	24 (43.6%)
	Other	24 (43.6%)
	BOOP	1 (1.8%)
HRCT progress (first to last scan) (n=48)	Improved	3 (5.5%)
	Static	35 (63,6%)
	Worsened	10 (18,1%)

The pulmonary function test findings for the cohort are shown in table 6. The minimum initial FVC was 0.70L and the maximum was 3.74L, while the corresponding results for the last FVC were 0.66l and 3.36l respectively. In terms of FEV1 the minimum first FEV1 was 0.69L and the maximum was 3.09L, while the minimum last FEV1 was 0.55L, with a maximum of 2.93L. We defined a difference of 10% between first and last pulmonary function tests as being required to categorise a patient's pulmonary function as having improved or deteriorated. However, if a difference of less than 10% were also considered, 34 (61.8%) patients had a deterioration in FVC,

while 19 (34.5%) had an improvement in FVC. The median change in FVC was a decrease of 0.09l (p=0.011). Similarly, the last FEV1 was significantly lower than the first FEV1 (median decrease 0.15L, p=0.001). Comparing individual pairs (not using the predefined 10% cut-off), the last FEV1 was lower than the first FEV1 in 39 (70.9%) cases, with an improvement in only 15 (27.3%).

Table 6: Lung function test trends		
		n (%)
FVC trend	Static	28 (50.9%)
	Improved	7 (12.7%)
	Decline	20 (36.4%)
FEV1 trend	Static	21 (38.2%)
	Improved	8 (14.5%)
	Decline	26 (47.3%)

A total of 43 patients had 6-minute walk tests performed. The median initial 6-minute walk test was 430m (IQR 350m-487m). Of these patients 31 had a subsequent 6-minute walk test. The median distance for the final 6-minute walk test was 420m (IQR 360m-470m). The difference between first and last 6-minute walk test was not statistically significant (p=0.189). Of note 20 (64.5%) patients had a deterioration in 6-minute walk test, while 11 (35.5%) had an improvement.

The diffusing capacity of the lungs for carbon monoxide (DLCO) was measured at least once in 34 patients, with 13 having a repeat test. The median initial DLCO was 3.5L (IQR 3.1 - 4.5), last DLCO 3.4L (IQR 3.1 – 3.9) and difference between first and last DLCO -2.1% (IQR -9.4% - 4.1%). Of the patients with more than one DLCO results, 9 (69.2%) had no change, 3 (23.1%) had a deterioration in DLCO and 1 (7.7%) had an improvement in DLCO.

The median ESR at first presentation was 35 (IQR 20 – 60) while the median CRP was 7.0 (IQR 2.0 - 13.4).

Discussion:

The prevalence of ILD in this study was 37.7% which is similar to that described in another South African study from Gauteng Province (40%) and in studies from Europe (~35%) but may be lower than in studies from North America (~52%) (14, 15). These findings suggest that ILD is common in

patients with SSc in Sub-Saharan Africa and all patients with SSc should be screened for pulmonary involvement.

The median age at time of diagnosis of ILD was 51 years in the present cohort, which is slightly older than that reported in the other South African cohort (44 years) (14). Our median age was however, broadly similar to that seen in international studies. A US cohort study from 1997 to 2013, including 156 SSc-ILD patients, reported a mean age at diagnosis of 54.5 (±13.2) years (16), which was consistent with results from two longitudinal US cohort studies assessing 225 SSc-ILD patients (mean age: 54 years) (17). Similarly, the median age of SSc patients with severe ILD, identified as patients with an FVC <60% from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry in the United States and Canada, was estimated to be 52.5 years (18).

The majority (87%) of patients in this study were female, which is in keeping with global findings. Most of the patients (56%) in this study were, however, of Indian ethnicity, which is contrary to what has been described in other studies. The most likely explanation is the high Indian population in KwaZulu-Natal and Durban in particular. The Indian/Asian population makes up 24% of the population of Durban, and 8% of the population of KwaZulu-Natal(19). This requires further study as genetic predisposition may have a role. In the study from Gauteng, the majority of patients were female (87.4%) and of black ethnicity (86.8%). Caucasians represent 2.7%, Indians 3.3% and mixed race individuals 7.2% (14) . Internationally similar gender ratios were observed in patients with SSc and SSc-ILD, with a female predominance in both Europe (75–82%) and North America (≥69%). Data from North America suggest that SSc-ILD and associated complications are observed most frequently in Caucasian patients (15).

In this study a significant proportion of patients had overlap with other connective tissues diseases. Systemic lupus erythematosus had the highest incidence of 18%, which may be due to the high prevalence of SLE in South Africa. There is limited data about the prevalence of other connective tissue diseases in patients with scleroderma ILD. In an Israeli study (16) examining the incidence of other connective tissue diseases in scleroderma patients (including forty patients who satisfied the criteria for scleroderma overlap syndrome), the incidence of additional connective tissue diseases in the whole group and in the overlap group respectively was 11.5% and 47.5% for dermatomyositis and polymyositis, 10.3% and 42.5% for Sjogren's syndrome, 3.6% and 15.4% for rheumatoid arthritis and 1.2% and 5% for systemic lupus erythematosus.

We found that most patients presented with skin thickening and Raynaud's phenomena, 49 (89.1%) and 46 (83.6%) respectively. This is similar to the Gauteng study which reported Raynaud's phenomenon (82.8%) and nail fold capillary changes (70.2%) as common presenting symptoms. In our study 47 patients (85.4%) presented with dyspnoea, with most (58.2%) having Grade II dyspnoea at the time of presentation. This may indicate that dyspnoea is the best symptom marker of the development of ILD and can be used as a good and cheap screening tool.

ANA was positive in 50 of 54 patients (92.6%), anti-Scl-70 antibodies were positive in 21 of 45 (46.7%) patients and anti-centromere antibodies were positive in only 1 of 14 patients (7.1%). In the Gauteng study the ANA was positive in 88.1% of cases with the commonest ANA patterns were being speckled (40.6%), and nuclear (31.6%). Only 7.5% had a positive ACA, while 19% were anti-topoisomerase positive (14). This may indicate that the development of ILD in systemic sclerosis is more likely in patients with positive anti-Scl-70 and negative anticentromere antibodies. This is similar to what has been found in international studies where the variables that predicted clinically significant pulmonary fibrosis development were dcSSc, older age at onset, lower forced vital capacity and DLCO, and the presence of anti-Scleroderma-70 antibody. The presence of anticentromere antibodies was protective (17). Anti-Scl-70 antibodies are also associated with worse prognosis, while ACA is associated with better prognosis (18).

In this study the majority of patients received cyclophosphamide as the main immunosuppressant for induction therapy followed by azathioprine. None in the present cohort received any biological therapy, stem cell therapy or lung transplantation. This was due to resource limitations. In the Gauteng study, corticosteroids were used in conjunction with cyclophosphamide as induction therapy followed by maintenance with either azathioprine or mycophenolate mofetil in 59.3% of ILD patients. Internationally in the EUSTAR study (which included 3778/11,496 patients with SSc-ILD (33%)), glucocorticoids (GC) monotherapy was prescribed in 30,6% of patients, GC combination plus cyclophosphamide (CYC) in 11.9%, azathioprine in 9.2%, methotrexate in 8.7%, and mycophenolate mofetil in 7.3% (6). The regimen used in our study compares favorably with regimens used elsewhere. Of note, in our cohort corticosteroids were not included. MMF was less frequently used as induction therapy despite a more favorable side effect profile compared to cyclophosphamide. The reasons for this need to be interrogated further, with consideration given to future use of MMF.

The most common finding on HRCT in our study was a UIP pattern. This may be due to late presentation of patients. This is dissimilar to the international literature where typical CT findings were ground glass opacification with an admixture of pulmonary fibrosis consistent with the NSIP

pattern. Honeycomb cystic changes are reported in 11% to 37% of patients with scleroderma-ILD (20). This is unlike other patients with NSIP, who have little or no cystic change. As honeycomb cystic change is typically a marker for UIP and pulmonary fibrosis. These findings suggest that patients with scleroderma-ILD disease may have a mixture (or overlap) of UIP and NSIP patterns.

When assessing longitudinal impact on pulmonary function using a change in FVC of 10%, most patients remained static, with approximately one third deteriorating. In a study that tracked lung function over a mean of 6.4±4.2 years, patients underwent a median of 5 PFTs during the follow up (21). While there was no significant decline in FVC overall during the study period (-0.1±0.3%/year, p = 0.71), 29% of patients experienced a significant decline of FVC of more than 10% from baseline after 6 years of follow up. In another study of 105 patients (45 diffuse SSc; median disease duration 2.0 years), 23 (23%) had an FVC of <80% predicted, and 60 (59%) had a DLCO of <80% predicted. Over 72±46 months, 29 (28%) patients displayed a decrease of ≥10% in FVC, 39 (40%) of 98 patients displayed a DLCO decline and 19 (18%) patients displayed a decrease of ≥20% in FVC. On multivariate analysis, diffuse SSc was a significant predictor for a decrease of ≥10% in FVC (p=0.01) (22). This shows that the majority of patients remain static or improve. Maintaining lung function is a positive outcome.

Limitations:

This was a retrospective review of electronic data and only data captured and available could be analysed. It was a small sample size. The small sample size as well as missing data may have biased any associations. However, scleroderma-ILD is a disease with a very low prevalence; hence smaller sample sizes are to be expected. There is the possibility of overestimation of prevalence as the study was conducted in a specialized clinic in the major referral hospital for the province. This may have resulted in referral bias. There may also have been patients with interstitial lung disease, who were missed because they were asymptomatic. Testing and follow-up intervals were not standardized which is another potential source of bias. Patients had different durations of follow up. Repeat HRCT scans were based on clinical judgment by the treating physician and was not standardised.

Conclusion:

This is the second study, to our knowledge, in South Africa, to report on the demographics and treatment of scleroderma-ILD in a multiracial cohort. While age and gender distribution are

consistent with global data, there is apparently a high prevalence of scleroderma–ILD among South Africans. UIP is the dominant radiological pattern. Cough and dyspnoea could be used as good screening tools for early detection of scleroderma–ILD. The use of cyclophosphamide and azathioprine appears to prevent disease progression. Increased utilisation of MMF should be considered. Further prospective multi-centre randomised controlled trials are required in this field to determine the optimal drug treatment to manage scleroderma-ILD.

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Part 3

Appendix 1: The final Study Protocol:

Appendix 1

The final Study Protocol

Title of study

Prevalence and outcomes of scleroderma associated interstitial lung disease at a tertiary level hospital in KwaZulu Natal, South Africa: A retrospective review.

Student: Dr/ SALAH TANISH (216033442)

Supervisor: Professor KENNEDY NYAMANDE

2.2 Identify the problem that is motivating your research.

Interstitial lung disease (ILD) is one of the most serious complications among patients with scleroderma, and despite advances in the understanding of the pathogenesis and treatment of the disease there is still significant morbidity and mortality. Pulmonary function test and high resolution CT scan play a central role in the diagnosis of interstitial lung disease and should be monitored routinely. Although certain subgroups of scleroderma patients seem to be at higher risk for developing intestinal lung disease, we do not have clear biomarkers for which patients will develop the disease or have disease progression. Treatment modalities that are often used with success in other autoimmune diseases have proven less beneficial in scleroderma associated interstitial lung disease. Cyclophosphamide remains the best studied agent and should be considered for any patient with progressive scleroderma associated interstitial lung disease. Newer investigational treatments such as rituximab, pirfenidone and HSCT may become options as further studies shed light on their potential benefit. Further understanding of the pathogenesis and molecular mediators will ultimately lead to novel treatment targets to modify the course of scleroderma associated interstitial lung disease.

2.3 What is the research question or the hypothesis?

Scleroderma associated interstitial lung disease frequency, spectrum of disease radiological features and clinical outcomes in Kwa Zulu Natal South Africa are similar to what has been described in the international data.

The aim of this study?

To determine the patient profile and treatment outcomes of patients that develop scleroderma associated interstitial lung disease in the South African context

The objectives of the study.

a. To determine the prevalence of patients that develop interstitial lung disease in scleroderma.
b. To describe the demographic profile of the study participants
c. To examine the specific patterns of interstitial lung disease on HRCT scan
d. To examine the management options that patients were placed on for interstitial lung disease and treatment specific outcomes.
e. To assess the positive anti-scleroderma antibodies and anticentromere antibodies and development of interstitial lung disease.
f. To assess pulmonary function test (PFT) parameters before and after treatment

g. To assess chest radiograph finding of patients with interstitial lung disease

h. To determine if there is any increased risk with HIV

Background and Literature review

Interstitial lung disease (ILD) is a prevalent but worrisome implication in scleroderma. It is now the leading cause of morbidity and mortality since the dramatic reduction in death caused by scleroderma renal crisis [1].. However, the pathogenesis remains unknown. Most observers suggest that lung injury induce microvascular damage and immunologically-mediated inflammation [2].. As oxidative stress and leukotrienes-lipoxins imbalance is observed in interstitial lung disease patients, a series of proinflammatory and profibrotic cytokines are also found. Possible biomarkers including SP-D, KL-6, Caveolin-1, IL-6, IL-1 may be useful index for diagnosis and progression, which also suggest the potential mechanism [3]. There are also some studies focusing the relationship between gastroesophageal reflux (GER) and scleroderma associated interstitial lung disease, which partly explains the mechanism from a new perspective.

Clinical Features and Diagnosis

Scleroderma associated interstitial lung disease is known as a rare and potentially lethal and devastating autoimmune disease. The two main complaints in scleroderma associated interstitial lung disease patient are usually dyspnea on exertion and nonproductive cough. However, these presentations often occur at a late stage. On physical examination, the most common abnormality is the presence of bi-basilar dry "Velcro" crackles at lung basses dyspnea is the main manifestation, scleroderma associated interstitial lung disease should be differentiated from pulmonary hypertension, myocardial involvement, deconditioning, aspiration pneumonitis, interstitial pulmonary fibrosis and idiopathic interstitial lung disease [4].

Up to now, there are no definite standard diagnostic criteria. The diagnosis relies on chest high resolution computed tomography (HRCT), pulmonary function testing, Bronchoalveolar lavage (BAL) fluid analysis and lung biopsy. In a case reported by Kristine Phillips, the patient was mainly diagnosed by HRCT, pulmonary function testing and lung biopsy [5]. Conventional chest radiography can show linear shadow, even a "Honey comb" reticular appearance at the periphery of the lung at the bases. More effectively, HRCT abnormalities have been shown in nearly 90% of scleroderma associated interstitial lung disease patients similar to that found at autopsy. These abnormalities include ground glass (an evidence of alveolitis), sub-pleural lines, honeycombing and parenchymal bands (symptoms of irreversible pulmonary fibrosis) [6]. Pulmonary function testing often reveal a restrictive ventilatory defect with a reduction in total lung capacity (TLC), vital capacity (VC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO).BAL fluid from scleroderma associated interstitial lung disease patients has been investigated with an increased percentage of neutrophils, eosinophils and lymphocytes, often referred to as "alveolitis". This kind of alveolitis not only proves active lung disease in scleroderma, but also has prognostic value. BAL cells also express a large spectrum of factors from cytokines, chemokines, and growth factors to coagulation factors, which to some extent explain the inflammation and fibrosis at autopsy [7].Histopathologically, the autopsy in majority is characterized by a pattern termed as nonspecific interstitial pneumonia (NSIP): varying degrees of pulmonary inflammation and fibrosis. The early stage being primarily inflammatory is commonly termed as cellular NSIP, while others being primarily fibrotic known as fibrotic NSIP. The minority of scleroderma associated

interstitial lung disease patients show a pattern of usual interstitial pneumonia (UIP) characterized by a nonuniform distribution of alternating zones of dense fibrosis, fibroblast foci, scant inflammation, normal lung and honeycomb change [8].

The decision of who requires treatment in the scleroderma associated interstitial lung disease is not straightforward. An effective therapeutic regimen

Should prevent progression to fibrosis. Therefore, treatments should target disease when a reversible component is present. Defining this reversible component can be difficult but new methodologies such as exhaled nitric oxide [9] and CT scan computer-aided diagnostic tools [10] and composite scoring systems [11] are being developed. In general, appropriate candidates for therapy are those who have early stage lung disease, have ground glass opacities on CT scan or who are demonstrating progression of disease. Therapy of scleroderma will evolve as better understanding of the pathophysiology of scleroderma progresses. Similar to problems understanding genetic predisposition to scleroderma, a significant barrier to successful development of therapies is defining scleroderma subgroups. At present, therapeutic interventions are primarily immunosuppressant in nature although, increasingly, anti-fibrotic agents are also being investigated. While there are several drugs that have been evaluated in small series or with retrospective analyses, only a small number of drugs have been assessed via randomized controlled studies. Currently, few therapeutic options exist for patients with scleroderma associated interstitial lung disease.

Conclusion

Scleroderma associated interstitial lung disease is a group of lung diseases affecting the interstitium and alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and per lymphatic tissues. Though the mechanism remains unknown, some achievements have been made. It’s widely accepted as a disease chartered by inflammatory reaction and immune abnormalities. Nowadays, new biomarkers including SPD, KL-6, Caveolin-1, IL-6, and IL-1 are illustrated to play a potential role in the pathogenesis of scleroderma associated interstitial lung disease, while they are commonly received as prognostic index. We expect further study towards the expand system of immunologic and molecular change in scleroderma associated interstitial lung disease patients to find an efficient way to prevent or improve the condition of lung tissue fibrosis.

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Research design: retrospective observational descriptive study.

Study population: Adults (age >18yrs and older) diagnosed with scleroderma with interstitial lung disease at Inkosi Albert Luthuli Central Hospital in KwaZulu Natal

6. Study sample:

Patients (18 years and older) who are diagnosed with scleroderma associated interstitial lung disease during the period between January 2010 and December 2016.

Sampling technique: electronic chart review

Aim for a sample of 100 patients

Sampling strategy

The study population will include patients (age 18 years and older) who have been diagnosed with scleroderma with interstitial lung disease in the period between January 2010 and December 2016.

Variables

Variables that will be recorded include:

1.Age

2.gender

3.race,

5. Anti-centromere antibodies

6. Anti scl 70 antibodies

7.Clinical presentation and duration of symptoms.

8. Radiological findings including CXR and HRCT

9.Histological findings if done

10.Pulmonary function testing

11.Medications

12.Outcomes after treatment

13. HIV status including CD4 count and Viral Load

14. CRP and ESR level

Inclusion Criteria

All ADULTS (18 years and older) diagnosed with scleroderma with interstitial lung disease at the Department of pulmonology and rheumatology clinics at Inkosi Albert Luthuli Central Hospital between 01/01/2010 to 31/12/2016.

Exclusion criteria

-Cases where electronic data sets cannot be retrieved.

-Patients with other connective tissue diseases.

-Patient in whom the diagnosis of scleroderma or interstitial lung disease is doubtful.

Data Collection Methods and Tools

Retrospective electronic chart review between January 2010 to December 2016 in the Department of pulmonology and rheumatology at Inkosi Albert Luthuli Central Hospital, Durban, South Africa.

Research method: data collection sheet

Data analysis techniques

Sample Size determination

This study seeks to determine the incidence and prevalence of interstitial lung disease (ILD) in patients visiting the Rheumatology and Pulmonology clinic at Inkosi Albert Luthuli central Hospital, in Durban South Africa. The following statistical parameter were used to arrive at minimum sample size with statistic power 80%, type 1 (α) error = 0.05 (this is the probability of falsely rejecting the null hypothesis), type 2 (β) error =0.2 (probability falsely failing to reject the null hypothesis). On the basis of the above statistical parameters a minimum sample size of 100mmk was determined. It is important to ensure that a sufficient number of patient with HIV are included in this study as well as both male and female. In the sampling of patients, it is also important that patients are recruited from different age-groups ranging from 18 to 60 years old and a good representation of different ethnic groups is important such as White, African, Indian and Colored

Statistical analysis

Continuous variables will expressed as mean ± standard deviation or median (interquartile range) and will be compered using Student's t test or Wilcoxon test as appropriate. Categorical variables will be expressed as proportion and compared using Chi-square test or Fisher's exact test as appropriate, the clinical outcomes for the patient will be binary in nature, i.e. positive or negative for interstitial lung disease (ILD). Therefore a binary logistic regression model well be used to predict the relative risk of interstitial lung disease (ILD) based on independent variable collected in this study. SPSS version 25 will be used for the analysis and statistical significance will be at $P < 0.05$.

Study location

The study location will include patients (age 18 years and older) who diagnosed with scleroderma with interstitial lung disease at the Inkosi Albert Luthuli Central Hospital.

Part 4

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.

- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

AJTCCM is a medical journal covering all aspects of respiratory health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published

previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summaries the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 – 25 references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Click Here for an example of a good abstract.

Case reports/Scientific letters/Short reports

These include side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Contributors are encouraged to write to the Editor about possible papers to be considered for review, and where appropriate a review outline will be submitted to experts in the field for consideration before a full review is commissioned. It is expected that an author or authors have substantial experience and track record in the field that the review is about.

*Guideline word limit: 3 500 words (*unless an alternative word limit has been arranged with the Chief Editor)

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Contributors are encouraged to include tables and figures in their reviews to keep to the maximum word count.

Guidelines

Must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

- A structured abstract not exceeding 250 words
- Recommended sub-headings: Background, Recommendations, Conclusion is required.
- Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarized in a Table of Contents.
- References, appendices, figures and tables must be kept to a minimum.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the AJTCCM or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table

- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.

- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.

- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355.http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)

  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard) (4):
  Volume number
  SA: SA Law Reports
  11: Page or section number
  (N) : In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
  NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *AJTCCM* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form [forthcoming]
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
  - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at AJTCCM.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion

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Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format,

spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

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Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

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- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

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Send an email to publishing@hmpg.co.za, including the following details:

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- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

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As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (jpeg or pdf). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Part 5

Appendix 3: Ethical approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

05 June 2019

Dr S Tanish (216033442)
School of Clinical Medicine
College of Health Sciences
salahtonish@gmail.com

Dear Dr Tanish

Protocol: Prevalence and outcomes of scleroderma associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective review.
Degree: MMed

BREC REF: BE602/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received 26 September 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 04 June 2019 to BREC letter dated 24 May 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 05 June 2019. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **05 June 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **11 June 2019.**

Yours sincerely

[redacted]

Prof D Wassenaar
Acting Chair: Biomedical Research Ethics Committee

Supervisor: nyamandek@ukzn.ac.za postgrad admin: konar@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

24 June 2021

Dr S Tanish (216033442)
School of Clinical Medicine
College of Health Sciences
salahtonish@gmail.com

Dear Dr Tanish

Protocol: Prevalence and outcomes of scleroderma associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective review.
Degree: MMed
BREC REF: BE602/18

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**05 June 2021**
Expiration of Ethical Approval:	**04 June 2022**

I wish to advise you that your application for recertification received on 11 May 2021 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC). The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 13 July 2021.

Yours sincerely

[redacted]
.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ialch.co.za
www.kznhealth.gov.za

DIRECTORATE:
Office of The Medical Manager
IALCH

11 November 2018

Dr S Tanish (216033442)
School of Clinical Medicine
College of Health Sciences

Dear Dr Tanish

Re: Approved Research: Ref No: BE 602/18: Prevalence and outcomes of scleroderma associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective review.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted] Dr Nensha Tatiraal

Acting

Dr L P Mtshali /PP
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: [redacted]
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

Ref: KZ_201905_016

Dear Dr S Tanish
(UKZN)

Subject: Approval of a Research Proposal:

1. The research proposal titled **'Prevalence and outcomes of scleroderma associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective review'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:

   a. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   b. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   c. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete.*

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 03/06/19.

Part 6

Appendix 4: Data collection tools:

KZ Numbers	Age	Gender	Race	Comorbidity	PHT	
Presenting complaints(At time of Diagnosis)	dyspnea grad	Organ system involved	ANA	titer	Anti-centromere antibodies	
titer	Anti-Scl 70 antibodies	titer	HIV STATUS	Treatment	CD4	
ARVS	FVC: Initial	FVC: Last	Percentage Change	FVC trend	FEV1: First	
FEV1: Last	Percentage Change	FEV 1trend	% fev1:fvc :first	% fev1:fvc Last	Percentage Change	
%fev1:fvc trend	HRCT 1ST	others	HRCT last	DRUGS TYPES	SYMPTOM OUTCOME	
skin tightness	raynaude phenomenon	dysphagia	dyspnea	cough	6 MINUTE WALK TEST INTIAL	
6 MINUTE WALK TEST LAST	6 NINUTE trend	CO DIFFUSION INTIAL	CO DIFFUSION LAST	CO diffusion trend	ESR	CRP

Appendix 5: Raw data:

KZ Numbers	Age	Gender	Race	Comorbidity	PHT
kz00002209	62	2	1	2	1
kz00507556	33	2	1	1	1
kz00503585	56	2	1	7	7
KZ00503067	55	2	2	1	1
kz00502417	50	2	1	1	1
kz00502123	35	2	2	1	1
kz0050373152	41	2	1	2	1
kz00016084	51	2	2	2	1
kz00017461	40	2	2	1	1
kz00022272	63	2	2	1	1
KZ00024425	36	2	2	4	1
kz00028049	50	2	1	7	7(28+10)
kz00036347	54	2	2	2,7&8	7 (17+10)
kz00041897	61	1	2	1	1
kz00060884	41	2	1	3&7	7(30+10)
kz00064742	58	2	2	2	1
kz00070397	41	2	2	7	15+10
kz00071102	57	2	2	1	1
kz00082573	48	1	2	7	50+10
kz00098123	70	2	1	8	
kz00101670	53	1	1	7	35+10
kz00103727	45	2	2	1	
kz00123366	51	2	1	7&8	66+10
kz00132203	39	2	1	1	
kz001234874	63	1	1	7	33+10
kz00140403	72	2	2	4	
kz00142513	41	2	1	1	
kz00147614	60	2	2	7	31+10
kz00148567	34	2	1	3	
kz00154485	61	2	2	6	
kz00163514	61	2	1	3&8	
kz00169696	43	1	1	1	
kz00186216	51	2	1	1	
kz00187873	66	2	1	1	
kz00202034	69	2	3	1	
kz00202951	33	2	1	1	
KZ00204895	48	2	2	2,7	67+10
KZ00223575	61	2	1	1	
kz00234566	66	2	1	1,7	
kz002417441	48	2	1	1	
kz00242856	49	2	2	7	33+10
kz00260241	40	2	1	2,7	36+10

kz00264100	55	2	1	1	
kz00264987	62	2	1	1	
kz00281792	54	1	1	7	32+10
kz00297231	23	2	1	1,7	
kz00302291	33	2	1	3	
kz00305332	51	1	1	1	
kz00305814	44	2	2	3,4	
kz00306906	47	2	2	1	
kz00317951	55	2	2	2,7	38+10
kz00323731	55	2	2	2,7	90+10
kz00324109	58	2	2	1	
kz00326755	52	2	2	1	
kz00345850	42	2	3	2	

Presenting complaints(At time of Diagnosis)	dyspnea grad	Organ system involved	ANA	titer	Anti-centromere antibodies
2	1	1&2	2	200	3
2,3&5	4	1&2	2	640	3
3	1	1&2	2	2560	1
2.3.4.&5	3	1,2,&3	2	40	2
3,4,5	4	1.2&3	2	2560	3
5	3	1&2	2	2560	3
4.&5	5	1&2	2	640	3
2.3.4.&5	3	1.2&3	2	800	1
2.3&6	1	1&2	2	160	3
2.&3	1	1&2	2	1	1
2.3.4.5&6	3	1&2	2	2560	1
2.3.&5	3	1&2	2	800	1
2,3,5&6	3	1.2&4	2	160	1
2.3.5&6	3	1.2&3	2	50	3
2.3.4.5&6	3	1&2	2	3200	3
2&6	1	1&2	2	3200	3
2.3.,4.5&6	3	1.2&3	2	800	3
2.3.4&5	3	1.2.&3	2	160	3
2.3&5	3	1.2	2	3200	3
2.4&5	3	1.2&3	2	3200	1
2.,3&5	3	1&2	2	3200	3
2.3.4&5	3	1,2&3	2	800	3
2.4.5&6	2	1.2&4	2	3200	3
2.3&5	2	1&2	2	40	3
2.3.4.5&6	2	1.2&3	2	800	3
2,3,5&6	2	1&2	2	200	3
2.3.4&5	3	1.2&3	2	3200	3

2.3&5	4	1&2	2	200	3
2.3&5	3	1&2	2	3200	3
2.3.4&5	3	1,2&3	2	200	1
2,3,4,5&6	2	1.2&3	1		1
2,3&4	3	1,%2	2	2560	3
2,5&6	3	1&2	1		1
2&5	3	1&2	2	650	3
2,3,4,&5	3	1,2,3	2	640	3
2,3,5	2	1,2	2	2560	3
2,5	4	1,2,4	2	2560	3
2,3,4,5	3	1,2,3	2	640	3
2,3,4	4	1,3	1		1
2,3,5	2	1,2	2	640	3
2.3.5	4	1,2	2	160	3
2,3,5,6	3	1,2,3	2	2560	3
2,3,5,6	3	1,2	1		1
3	3	1,2	2	160	3
2,3,5,6	3	1,2	2	640	3
2,3,4,5	3	1,2,3	2	2560	3
2,3,5	3	1.2	2	2560	3
2,3,4		1,2	2	2560	3
2,3,4,5,6	3	1,2,3	2	2560	3
2,3		1,2	2	2560	3
2.3		1,2	2	2560	3
3,4,5	3	1,2,3	3	2560	1
2,3,5,6	4	1,2	2	2560	3
2,3,5	3	1.2	2	2560	3
2,3,5	3	1,2	2	640	3

titer	Anti-Scl 70 antibodies	titer	HIV STATUS	Treatment	CD4
	1		1		
	2	320	1		
	1		1		
240	1		1		
	2	320	1		
	1		1		
	3		1		
	2	62	1		
	2		1		
	1		1		
	1		1		
	1		1		

1		1		
1		1		
2	320	1		
2		1		
3		1		
1		1		
1		1		
1		1		
1		2	yes	630
2		1		
1		1		
2	38	2	yes	602
2		1		
1		1		
2		1		
2		1		
1		1		
1		1		
1		1		
2		1		
1		1		
2		1		
3		1		
2	133	1		
1		1		
2		1		
1		1		
3		1		
3		1		
3		1		
1		1		
2		1		
3		1		
3		1		
2	11,4	1		
2	141	2	yes	568
3		1		
3		1		
2		1		
1		1		
2	14	1		
2	224	1		
2	224	1		

ARVS	FVC: Initial	FVC: Last	Percentage Change	FVC trend	FEV1: First
	1.59	1.63	2,5%	2	1.27
	1,11	0,71	36%	3	1.02
	1,42	1,42	0%	2	1,24
	1,74	1,54	11%	3	1.29
	1.82	1.85	1.65%	2	1,49
	2,38	2,43	2%	2	1,87
	0.7	0,72	2.80%	2	0,69
	2.76	2,99	14%	1	2,10
	1.28	1,40	9%	1	1,14
	2.82	2,45	13%	3	2,24
	1,92	1,86	3%	2	1,70
	1,55	1.63	5%	2	1,44
	1,32	1.64	24.20%	1	1,.08
	2.01	1,67	16.90%	3	1.57
	1,65	0,66	60%	1	1,53
	1,84	1,51	18%	3	1,84
	1,38	1,30	5.80%	2	1,33
	2,45	2,27	7,3%	2	1,93
	1.85	1,26	32%	3	1,46
	1,33	1.19	10,5%	3	1.07
FDC	3,74	2.08	44%	3	3.02
	1.32	0,78	40%	3	1,08
	1,59	1,86	16%	1	1,58
FDC	1,88	2,68	42%	1	1,87
	2,27	1,49	34%	3	1,83
	2,47	2,47	0%	2	2.01
	0,91	0,82	9,8%	3	0,76
	1.05	0,68	35%	3	1,00
	2,36	2,37	0,4%	2	2,07
	1,98	1,77	10%	3	1,73
	0,94	1,53	62%	1	0,93
	2,01	0,74	63%	3	1,75
	2,1	1,2	52%	3	2.13
	2,1	1,2	42%	3	1,58
	1,04	0,96	7,9%	2	0,85
	3,13	2,96	5,4%	2	3,09
	1,85	1,70	6,4%	2	1.41
	1,85	1,70	8,1%	2	1.4
	1,93	2,08	7,7%	2	1,66
	2.06	1,79	13%	3	1,79
	2,11	2,28	8%	2	1,6

	2,04	1,59	22%	3	1,53
	1,2	2	66%	1	1.18
	1,49	1,52	1,9%	2	1,32
	1,43	1,35	5,59%	2	1,40
	1,40	1,27	9,28%	3	2,59
	2,08	2,46	18%	1	2,03
fdc	2,17	2,43	11%	1	1,93
	2,31	2,27	1,7%	2	2,03
	3,06	3,36	9,8%	1	2,83
	1,72	1,22	29%	3	1,48
	1,84	1,44	21%	3	1,66
	1,54	1,35	12,3%	3	1,44
	1,86	1,76	5,3%	2	1,73
	1,96	1,94	1%	2	1.75

FEV1: Last	Percentage Change	FEV 1trend	% fev1:fvc :first	% fev1:fvc Last	Percentage Change
1.52	19%	1	79%	93%	17%
0.61	40.19%	1	92%	87,94%	4.41%
1,24	0%	2	87.53%	87.53%	0%
1,13	12.40%	3	73,87%	73,57%	0,4%
1,47	1,3%	2	82%	79.38%	3%
1,93	3%	2	78.16%	79.51%	1,7%
0,70	1,4%	2	97.41%	97.55%	0,143%
2,57	22%	1	76%	85%	11.84%
1,36	19%	1	89%	97.52%	9,5%
1.99	11%	3	77.80%	81.00%	4%
1,49	12%	3	94.64%	80.28%	15,1%
1,40	2,7%	2	93%	85.47%	8%
1,40	29.60%	1	88.18%	85%	3.50%
1,32	15.90%	3	93%	78%	16,12%
0,55	64%	3	92%	83%	9,7%
1,32	28.26%	3	100%	87.60%	12,4%
1,30	2,25%	2	96,68	99.5	2,9%
1,87	3%	2	78%	82%	5%
1,14	21%	3	92,6	90,83	1,91%
0,93	13%	3	80.63	77,47	4%
1.78	41%	3	80.68	85.87	6,4%
0,69	36%	3	81.6	88.59	8,5%
1,43	9%	2	85%	89%	4.70%
2,48	52%	1	99.26%	92.69%	6,6%

1,25	31%	3	81%	84%	3.70%
1,91	5%	2	89%	90.97%	2.20%
0,77	1,3%	2	82%	94%	14.60%
0,66	34%	3	95%	93,4%	0,16%
2,03	2%	2	87,76	88.72	1%
1,52	12%	3	87%	86%	1.10%
1,28	37%	1	98.94%	83.14%	15%
0,72	58%	3	87.28	97,04	11%
1,26	40%	3	75%	48%	36%
1,14	27%	3	75,23%	75%	0,3%
0,83	7,3%	2	46,14%	47.50%	2,4%
2,79	9,70%	2	98,66%	94.05%	4.60%
1,44	4,,2%	2	44.81%	47,49%	6,65%
1.2	14%	3	53,81%	50.18%	6,7%
1,75	5,4%	2	86,26%	83,74%	3,3%
1,56	12.84%	3	86,79	87.43%	0,74%
1,8	12,5%	1	74%	79%	6,75%
1,21	20%	3	75%	76,35%	1,8?%
1,57	33%	1	98,46%	78,65%	20%
1,19	9,8%	2	88,72%	78,39%	11%
1,25	10,7%	3	97,90%	92,91%	5%
1,15	55%	3	84%	89.93%	7%
2,17	6,2%	2	97,36%	88.31%	9,2%
1,87	3%	2	88,5%	77,18%	1,29%
1,96	3.40%	2	87,71%	86,46%	1,4%
2,93	3,5%	2	92,49%	86%	7%
0,90	39%	3	86%	73,98%	13%
1,15	30%	3	90,4%	79,17%	11%
1,19	17%	3	93%	80,92%	12%
1,43	17%	3	92,96%	80,92%	12%
1,68	4%	2	89,13%	86,76%	1,5%

%fev1:fvc		
trend	HRCT 1ST	others
1	4	interlobular and intralobular septal thickening with associated bronchiectasis 2
2	2	1
2	1	1
2	4	bronchiactasis2 / air trapping6
2	4	Ground glass opacities in the bases bilaterally 7/focal air taping 6

2	4	minimal focal traction bronchiectasis 2
2	2	1
1	4	Ground glass opacities in lower and upper lobe more in subpleural lower lobe
2	2	1
2	4	basal ground glass opacification
3	2	1
2	4	feature of early ILD
2	2	1.00%
3	4	lower lobe intralobular septal thickening with traction bronchiectasis
2	1	1%
3	4	feature of mixes acute and chronic ILD
2	2	
2	1	
2	2	
2	4	bilateral lower peripheral and dependent intra and inter lobular septal thickening
2	2	
2	1	
2	4	pulmonary interstitial fibrosis
2	2	
2	4	basal ground glass opacification
2	4	interlobular and intralobular septal thickening bilaterally in lower zone
1	2	
2	2	
2	2	
2	2	
3	2	
1	2	
3	4	bilateral intra and interlobular thickening
2	2	
2	4	lung cyst and nodules
2	4	mild ILD
2	2	
2	2	
2	4	ground glass and bronchiectasis changes in lower zone
2	4	alveolitis interlobular septal thickening
2	2	
1	4	bronchiectasis collapse of upper lope
3	2	
3	2	
2	4	basal interstitial interlobular thickening
2	4	patchy area of ground glass
2	1	
2	4	interstitial subpleural thickening

2	1,2	
2	1,2	
3	3,2	
3	4	
3	2	
3	4	calcified lung nodules
2	1	

skin tightness	Raynaud phenomenon	dysphagia	dyspnea	cough	6 MINUTE WALK TEST INTIAL
2	2	2	2	2	4
2	2	2	1	2	365m
2	2	2	2	2	4
2	2	2	2	2	350M
3	2	2	2	2	470M
1	2	2	1	2	390M
2	2	2	3	2	not done
2	2	2	1	2	350m
2	2	2	2	1	4
2	2	2	2	2	500m
2	2	2	2	2	560m
2	2	2	2	2	not done
2	2	3	2	2	50m
2	2	2	2	2	550m
2	2	3	2	2	no done
2	2	2	2	2	370m
2	2	2	2	2	595
2	2	2	2	2	470
2	2	2	2	2	510
2	2	2	2	2	350
2	2	2	2	2	480
2	2	2	2	2	420
2	2	3	2	2	4
3	2	2	2	2	530
3	2	2	3	3	4
2	2	2	2	2	4
3	2	2	3	3	470
3	2	2	3	2	340
2	2	2	2	2	460
2	2	2	2	2	525
2	2	3	3	3	300

2	2	2	2	2	435
2	2	2	2	2	460
2	2	2	2	2	380
1	1	1	1	2	380
1	1	1	1	2	4
2	2	2	2	2	200
2	2	2	2	2	430
2	2	2	2	2	430
2	2	2	2	2	460
2	2	2	2	2	4
3	3	3	3	3	487
3	2	2	2	2	440
2	2	2	2	2	470
2	2	2	2	2	4
2	2	2	1	2	385
2	2	2	1	2	300
3	2	2	1	2	4
2	2	2	1	1	495
2	2	2	1	2	600
3	3	3	3	3	325
2	2	2	2	2	420
2	2	2	1	1	330
2	2	2	2	2	410
2		2		2	305

6 MINUTE WALK TEST LAST	6 NINUTE trend	CO DIFFUSION INTIAL	CO DIFFUSION LAST	CO diffusion trend	ESR	CRP
4	4	4		4	29mm/hr	1.0mg/l
	4	4		4	53mm/hr	40mg/l
	2	1,63		4	52mm/hr	2mg/l
	4	4		4	10mm/hr	11mg/l
	4	2,72		4	46mm/hr	1mg/l
	4	6,75		4	28mm/hr	6mg/l
	4	4		4	106mm/l	76mg/l
460	1	4,83	4,44	3	48mm/hr	<1mg/l
4	4	4	4	4	12mm/hr	1mg/l
550m	1	3.2	4	4	7mm/hr	2mg/l
580	1	3,74	3,34	3	26mm/hr	2mg/l
not done	4	4,11	3,43	3	15mm/hr	10mg/l
not done	4	4	4	4	42mm/hr	20mg/l
540	3	3,4	3,4	2	9mm/hr	1.5mg/l
not done	4	3,62	4	4	115mm/hr	23mg/l
350	3	2,82	2,88	1	27mm/hr	2mg/l

440	3	4	4	4	61mm/hr	6.7mg/l
420	3	2,88	2,82	3	82mm/hr	1,4mg/l
360	3	4	4	4	9mm/hr	22 mg/l
200	3	3,51	4	4	92mm/hr	1,4mg/l
580	1	6,47	3,38	3	86,0mm/hr	0,7mg/l
395	3	1.42	4	4	44mm/hr	9mg/l
4	4	4	4	4	15mm/hr	48mg/l
4	4	4,2	4	4	98mm/hr	3,3mg/l
4	4	3,23	3,38	1	21mm/hr	10.2mg/l
4	4	4	4	4	77mm/hr	9,3mg/l
270	3	4	4	4	16mm/hr	5.5mg/l
270	3	4,	4	4	31mm/hr	1,3mg/l
475	1	4	4	4	108mm/h	0,2mg/l
400	3	3,48	3,73	3	14mm/hr	8mg/l
4	4	4	4	4	84mm/hr	15,7mg/l
440	1	2,59	4	4	22mm/hr	7mg/l
450	3	2,2	4	4	34mm/hr	12mg/l
4	4	4	4	4	46mm/hr	13,4mg/l
390	1	4	4	4	35mm/hr	3mg/l
4	4	7,15	4	4	8MM/HR	4MG/L
245	1	3.07	4	4	17MM/HR	4MG/L
400	3	4,14	4,04	3	18MM/HR	13,8MG/L
400	3	3,83	4	4	27mm/hr	27mg/l
450	2	5,01	4	4	20mm/hr	9mg/l
4	4	4	4	4	15mm/hr	0mg/l
4	4	3,68	4	4	36mm/hr	14mg/l
400	3	4	4	4	33mm/hr	10mg/l
490	1	4	4	4	23mm/hr	0mg/l
650	4	4	4	4	43mm/hr	6mg/l
200	4	2,11	4	4	85mm/hr	12mg/l
440	1	3.53	4	4	73mm/h	18mg/l
4	4	5,98	4	4	39mm/hr	18mg/l
4	4	4,81	4,98	1	33mm/hr	5mg/l
510	3	5,85	4	4	29mm/hr	11mg/l
4	4	3,08	2,88	3	48mm/hr	8mg/l
460	1	4,26	4	4	135mm/hr	3mg/l
310	3	4	4	4	39mm/hr	10mg/l
400	3	3,83	4	4	60mm/hr	4mg/l
470	3	3.05	3,49	1	59mm/hr	18mg/l