THE CLINICAL PROFILE, SEROLOGICAL PROFILE AND MANAGEMENT OF PATIENTS DIAGNOSED WITH SYSTEMIC SCLEROSIS IN SOUTH AFRICA.

A SINGLE CENTER EXPERIENCE

A Retrospective Descriptive Study

By

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Declaration

I, Nokwazi Shandu, declare that:

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Signature: Date:11 September 2023

Dedication

I dedicate this study to my family for their motivation, support and prayers.

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Table of Contents

List of tables

List of abbreviations

ACA	Anti-Centromere Antibodies
ACR	American College of Rheumatism
BREC	Biomedical Research Ethics Committee
CT	Computerized Tomography
EULAR	European League against Rheumatism
EUSTAR	European Scleroderma Trials and Research
GAVE	Gastric Antral vascular ectasia
GERD	Gastro-Esophageal Reflux Disease
HLA	Human Leukocyte Antigen
IALCH	Inkosi Albert Luthuli Central Hospital
KZN	KwaZulu-Natal
MCP	Metacarpophalangeal
PAH	Pulmonary Artery Hypertension
REDCap	Research Electronic Data Capture
RP	Raynaud's phenomenon
SA	South Africa
SSA	Sub-Saharan Africa
SSc	Systemic sclerosis
USA	United States of America

Abstract:

Systemic sclerosis (SSc) is a complex and clinically heterogeneous disease with protean clinical manifestations, a chronic and frequently progressive course, and significant disability and mortality. The disease is characterized by fibrosis of the skin, internal organs and vasculopathy. While it can affect every organ, there is marked variability in patterns of skin and organ involvement, rates of disease progression, response to treatment and survival.

The limited studies of SSc in South Africa (SA) have largely described the clinical manifestations and antibody profile in African patients. Since the last study from Durban in 1991 looking at the serological profile of SSc, there have been advances in serological and imaging investigations and therapeutics. Recent studies are predominantly from Johannesburg (JHB), and this study was conducted to look at the demographic profile, clinical characteristics and serological profile of patients with SSc in our local population. Inkosi Albert Luthuli Central Hospital (IALCH), a quaternary hospital, serves as a referral hospital for KwaZulu-Natal and part of the Eastern Cape. The Rheumatology Department provides outpatient and inpatient service for patients with SSc. Given the demography of KZN, the majority of patients attending the clinic are Indian and African Blacks subjects and this study brings the opportunity to document SSc in these populations.

A retrospective chart review of the electronic records of all patients with SSc attending the rheumatology clinic IALCH was undertaken for the period January 2010 to December 2020. All patients with confirmed diagnosis of SSc and at least two visits to the clinic were included. Comparisons were made between limited and diffuse SSc and African and Indian patients using two-sided Fisher's exact tests, Student's t-tests and the Mann-Whitney U test for normally distributed and skewed numerical variables, respectively. This is the first study to report the differences in presentation of SSc between African and Indian patients in SA, which is reflective of the KZN population. African patients were significantly younger than Indian patients and more likely to have diffuse disease and a shorter disease duration. Interstitial lung disease and PAH, which are associated with poor outcomes, remain common manifestations, especially in diffuse disease. We confirm the absence of ACA in African patients; the mechanism of which requires further research.

Chapter 1: Literature review

1.1 Introduction

Systemic sclerosis (SSc) is an immune mediated rheumatic disease characterized by fibrosis of the skin, internal organs and vasculopathy. It can affect every organ (namely the heart, the lungs, kidneys, skin, vascular, musculoskeletal, gastrointestinal tract and the oral cavity), but there is marked variability in patterns of skin involvement, organ complications, rates of disease progression, response to treatment and survival (1, 2). Systemic sclerosis, also known as scleroderma, is defined as a complex and clinically heterogeneous disease with protean clinical manifestations, a chronic and frequently progressive course, and significant disability and mortality (1).

Systemic sclerosis is classified into two major disease subsets based on the extent of skin involvement; limited cutaneous SSc which refers to restricted skin involvement affecting the limbs distal to the elbows or knees, with or without face and neck involvement and diffuse SSc referring to skin involvement proximal to elbows and knees and proximal to metacarpophalangeal joints (3).

While in other autoimmune conditions, like rheumatoid arthritis and systemic lupus erythematosus (SLE), low socioeconomic status and deprivation is associated with increased morbidity and mortality (4, 5), studies from developed countries reveal that there is no association between the incidence and prevalence of SSc and socioeconomic status, and no association between the socioeconomic deprivation and mortality (6).

1.2 History of systemic sclerosis

Systemic sclerosis was first described in 1752 by Carlos Curzio, Giovambattista Fontanetti coined the term scleroderma in 1836, but the systemic nature of the disease was only highlighted in 1945 by Robert Goetz, and the term SSc was more widely used after that. Swiss artist Paul Klee (1879-1940) was the first famous person who was diagnosed with SSc after his death following a five year aggressive disease course (7, 8). There has been a dramatic improvement in the understanding of SSc following Klee's demise although many questions remain. The world scleroderma is derived from the

Greek word *skleros*, meaning hard or indurated and *derma* meaning skin, literally thickened skin. Following these publications, more clinicians became aware of the disease and its clinical presentation. Thus, several more cases were reported by the late nineteenth century physicians (8).

1.3 Epidemiology of systemic sclerosis

Systemic sclerosis globally affects around 3-24 per 100 000 persons (9), suggesting that causal factors, which likely include genetic susceptibility and several environmental factors, occur uncommonly (10). Systemic sclerosis is more common in women than in men. In developed countries, the ratio of women to men is 3:1 and can be as high as 7 - 8:1 (11-13). Age between 45 – 64 years, female sex, living in the United States of America (USA) and Australia, a positive family history and occupational exposure to silica have been found to be significant risk factors for SSc.(14)

In the European Scleroderma Trials and Research (EUSTAR) studies the mean age of the total cohort was 54.3 ± 13.8 years (11, 15). Patients with diffuse SSc were significantly younger than those with limited SSc (51.1 vs. 56.6 years, $p < 0.001$). There was a female preponderance with a female to male (F: M) ratio of 6.2:1. The majority of patients were Caucasians (89%), followed by Asians (6.2%) and Africans (2%)(11). In contrast, the recent Genome Research in African American Scleroderma Patients (GRASP) study showed that the African-Americans have a higher incidence of SSc, were younger at age of presentation (42 ± 13.5 years), but had a similar F:M ratio of 5:1 (11) African-American patients were also more likely to have diffuse (57%) rather than limited disease (43%) and a poorer prognosis compared to Caucasian/European patients (11).

In Western India, the mean age was even younger at 35 ± 10.5 years and the F:M ratio higher at 10:1 (16). In sub-Saharan Africa (SSA), the mean age at onset in a recent meta-analysis of 91 studies by Erzer was 36 years (range 4 to 77 years) with a female preponderance of 5.4:1 (15, 17, 18). A study from Johannesburg in SA in 2018 confirmed a similar mean age at onset (36.1 ± 13 years) and a female preponderance (F:M ratio 7:1) (13). Similar to African-American women (15), African patients in SSA, are more likely to have diffuse SSc, which was the presentation in more than 70% of patients (19).

Poor prognostic features include male gender, diffuse cutaneous subtype, pulmonary arterial hypertension (PAH) or scleroderma renal crisis and presence of Scl-70 antibody (10, 17). Cardiopulmonary involvement now supersedes the scleroderma renal crisis as a primary cause of SSc related death while malignancy remains the leading cause of non-SSc related death (10).

1.4 Clinical manifestations of systemic sclerosis

Systemic sclerosis may also overlap with other autoimmune disease, most commonly polymyositis, Sjogren's syndrome, autoimmune liver disease or SLE (1, 20). In limited cutaneous SSc, Raynaud's phenomenon generally precedes other disease manifestations, usually by years. Limited cutaneous subtype is associated with fibrosis of the skin affecting the acral parts of the body (face and limbs) distal to knees and elbows but proximal to metacarpophalangeal (MCP) joints. Although limited SSc has slow progression of skin fibrosis, it is not limited to skin involvement and is also associated with involvement of oesophagus and pulmonary arterial hypertension (21).

Many patients with limited cutaneous SSc display the characteristic Calcinosis cutis, Raynaud's phenomenon, oesophageal dysmotility, Sclerodactyly and mucocutaneous Telangiectasia (CREST) syndrome (7). The syndrome may also be present in diffuse SSc, but less commonly (22). Diffuse SSc is typically associated with diffuse skin induration starting in the fingers (sclerodactyly) and ascending from distal to proximal limbs and the trunk, and early development of interstitial lung disease (ILD) and renal involvement, which can happen in a short duration or both occur together (22).

Systemic sclerosis sine scleroderma (SSc) is a rare subset of SSc characterized by the total or partial absence of cutaneous manifestations with internal organ involvement and serologic abnormalities of SSc. It may be further classified as Type I or complete where cutaneous manifestations are absent, Type II or incomplete where there is the absence of sclerodactyly, but other cutaneous involvement (e.g. calcification, telangiectasia, pitting scars) may occur and Type III or delayed where the internal organ involvement occurs before the skin changes develop(23). The latter is more likely to be associated with systemic involvement such as renal crisis, pulmonary fibrosis and cardiomyopathy (23).

1.4.1 Skin and musculoskeletal involvement

The term scleroderma derives from the most characteristic feature of the disease, skin thickening, which is commonly associated with hypo- or hyperpigmentation and telangiectasia. It involves the trunk, extremities, face and neck and results in typical sharp facial features or “mask -like face”. The nasal alar and lips are thinned and radial furrowing around the mouth occurs. In severe cases eyelid movement is limited and the aperture of the mouth is reduced (microstomia) (24).

In early stages of the diffuse cutaneous subtype, the fingers are swollen or puffy, and skin becomes progressively indurated and thin especially on the fingertips where the formation of hard to heal erosions and ulcers may rapidly occur. Skin thickening decreases proximally. Sclerodactyly occurs with disease progression limiting the movement of fingers. Subcutaneous calcium deposits (calcinosis cutis) are sometimes present in the fingers and more often in limited variant.(25)

Raynaud’s phenomenon (RP) is characterized by episodes of reversible vasoconstriction of fingers and toes; it can also affect the tip of the nose or ear lobe. It is triggered by cold temperature, emotional stress or vibration and starts with digital pallor, cyanosis and hyperaemia which occurs spontaneously or with rewarming and is the most painful stage in the RP. If severe, RP can lead to digital ulceration and gangrene(26).

The common musculoskeletal features of SSc include carpal tunnel syndrome, generalized arthralgia and stiffness which are prominent early in the disease and maybe the presenting manifestations (27).

Systemic sclerosis is the most common connective tissue disease associated with inflammatory myositis and has been discovered in about 42% of individuals with overlap myositis (28).

Gastrointestinal tract involvement is the commonest organ manifestation in SSc and occurs in about 90% of individuals and affects all parts of the gastrointestinal tract. Microstomia and xerostomia are common and the oesophagus is most frequently involved with about 67% of individuals complaining of dysphagia, odynophagia, regurgitation,

chronic cough or hoarseness (29). The significant alteration of the stomach in SSc results in gastric antral vascular ectasia (GAVE) (29).

1.4.2 Cardiac involvement:

Involvement of the heart is often silent and asymptomatic affecting about 10-50% of patients and is more common in diffuse cutaneous SSc (30). It can be primary or secondary to pulmonary artery hypertension (PAH), ILD or renal involvement and is a marker of poor outcomes (31). Pericardial involvement is most common and includes pericarditis, pericardial effusions, constrictive pericarditis and rarely cardiac tamponade. Pericardial fibrosis can manifest as heart block (25, 30).

1.4.3 Pulmonary involvement:

Direct pulmonary involvement includes ILD with or without pulmonary arterial hypertension, PAH and less commonly pleural effusions. Indirect pulmonary complications include aspiration pneumonia secondary to oesophageal dysmotility, drug toxicity, malignancy, respiratory muscle weakness and restrictive lung defects (32). Interstitial lung disease in SSc has the highest case specific mortality amongst all autoimmune rheumatic diseases (33).

Although ILD is more common in diffuse SSc and pulmonary arterial hypertension in limited cutaneous SSc, any of the pulmonary manifestations may occur in either subset and the rate of progression of ILD is independent of the extent of skin involvement. Pulmonary involvement also may occur in the absence of skin disease (SSc), where the diagnosis is suggested by the presence of telangiectasia, RP and positive antinuclear antibodies. Interstitial lung disease and PAH have both been shown to be more frequent and more severe in African Americans compared to Caucasians (31).

In a study of 63 African patients with SSc in Johannesburg, SA, pulmonary fibrosis was found in 56% of the patients (34). In a subsequent study from the same center, ILD was reported in 40% of patients and predictors of ILD included disease duration and diffuse skin involvement (13). Pulmonary disease was the leading cause of death in these patients. The limitations of the study included the relatively small sample size and lack

of right heart catheterization to PAH (13). In Africa however, pulmonary arterial hypertension has been previously reported in 7.4% of 202 patients with scleroderma (35). While PAH has been associated with a poor outcomes, newer targeted therapy is associated with improved survival (36).

1.4.4 Renal involvement:

Renal involvement affects approximately 10% of SSc patients, is more commonly seen in diffuse SSc, usually occurs early in the disease and includes malignant hypertension in about 75% of the cases, renal dysfunction, and oliguria (13)). Scleroderma renal crisis is a serious complication and results from a vasculopathy of small vessels resulting in intimal proliferation of the vascular lumen and decrease in renal blood flow (37). Risk factors for renal crisis are Black race, male sex, diffuse disease and the use of high dose corticosteroids (38). Although the survival rate has improved dramatically with the development of angiotensin converting enzyme inhibitors (ACEI), the mortality rate with renal involvement remains high (38).

1.4.5 Neurological involvement:

Headaches, epilepsy and cognitive disorders are rare neurological manifestations of SSc. Patients present with peripheral neuromuscular disorders, namely myopathy, trigeminal neuralgia, motor and sensory neuropathy and carpal tunnel syndrome. Depression and anxiety have also been reported as secondary to the disease (39).

1.5 Serological profile of SSc

Systemic sclerosis is associated with several autoantibodies, these include anti-centromere (ACA), anti-topoisomerase1 (anti-Scl-70), anti-RNA polymerase III (ARA), anti-fibrillarin (U3-RNP), AntiTh/To, and anti-platelet derived growth factor receptor alpha (anti-PDGFR) antibodies (1). Antinuclear antibodies (ANA) are present in more than 90% of patients with SSc. Specific serological profiles correlate with patterns of clinical presentation and prognosis; the presence of ACA is associated with PAH, anti-Scl-70 with ILD and ARA antibodies with renal crisis (35). Anti-centromere antibodies (ACA) and anti-Scl-70 are mutually exclusive in SSc and the concomitant expression of both antibodies is extremely rare (40).

Anti-centromere antibodies maybe found in the serum of SSc patients years before the disease clinically manifests and continue to be expressed throughout the course of the disease (41). Patients with RP who also express ACA are at higher risk of developing SSc compared to those patients who have RP without ACA. Moreover, ACA are specific for SSc and rarely found in other autoimmune diseases or in healthy individuals (42).

The frequency of autoantibodies differs between African Americans and Caucasians, with anti-Scl-70 and anti-U3 and U1 RNP antibodies being more frequent in African Americans whereas in Caucasians the ACA, ARA and anti-Scl-70 antibodies are more frequent (13). Recent studies demonstrated a strong association between anti- fibrillarin antibodies and human leukocyte antigen (HLA) DRB1 *8:04. These genetic influences could be important factors contributing to differences in disease outcome (43).

A study done in Brazil confirmed the findings of the studies done previously in developed countries; ACA was associated with indicators of better prognosis whereas from anti-Sc70 antibody was associated with diffuse SS and higher severity (44).

1.6 Systemic sclerosis diagnostic classification

Compared to the 2010 criteria, the 2013 ACR/EULAR criteria are superior, more sensitive and inclusive and help with diagnosis of early disease (≤ 3 years duration) (45, 46). The sensitivity and specificity of the new criteria are 91% and 92%, respectively (47).

2013 ACR/ EULAR criteria for the classification of systemic sclerosis (scleroderma)

Item	Sub- item(s)	Weight/ score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count higher score)	Puffy fingers	2
Fingertip lesions(only count the higher score)	Digital tip ulcers	3
Telangiectasia	-	2
Abnormal nail fold capillaries	-	2
Raynaud's phenomenon	-	2
PAH and/or ILD (maximum score is 2)	PAH, ILD	2
Systemic sclerosis related autoantibodies (anti-centromere, anti-topoisomerase I (anti-Scl-70), anti-RNA polymerase III (maximum score is 3)	Anti-centromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3

*The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have scleroderma like disorder that better explains their manifestations (e.g. nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleroderma diabeticorum, scleromyxoedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic arthropathy).

The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of >/=9 are classified as having definite scleroderma.

1.7 Systemic sclerosis in South Africa

Limited studies describe the spectrum of clinical manifestations and antibody profile in South African subjects with systemic sclerosis. Progressive SSc was first reported in South African gold miners exposed to silica and while all patients with SSc were exposed to silica, not all the patients with SSc developed silicosis (26). Subsequently, studies have reported the clinical manifestations and antibody profile and clinical manifestations of SSc (13, 18, 47). Pulmonary manifestations (interstitial lung disease and pulmonary hypertension) were most common and the most frequent cause of death. Studies have also shown that anti-centromere antibodies were not present in African subjects (48). The South African studies have largely been conducted in African patients and there is limited information in South African Indian subjects.

1.8 Aim of the study:

To describe the clinical profile, serological profile and management of patients diagnosed with SSc attending Inkosi Albert Luthuli Central Hospital in KwaZulu-Natal, South Africa.

1.8.1 Objectives of the study:

1. To describe the frequency of organ involvement in patients with SSc seen at IALCH.
2. To describe the antibody profile in patients with SSc.
3. To determine the correlation between antibody profile and clinical manifestations.
4. To compare the clinical manifestations and antibody profile in African and Indian patients

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Chapter 2: A Submission ready manuscript

The manuscript is submitted according to the instructions for the International Journal of Rheumatology (Guidelines for Authorship in appendix)

Manuscript

The clinical and auto-antibody profile in systemic sclerosis in Kwa-Zulu Natal, South Africa: A single center experience

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Abstract

Background: Systemic sclerosis (SSc) has a high morbidity and mortality with ethnic differences in presentation and prognosis.

Objective: To describe the socio-demographic, clinical and antibody profile in patients with SSc in Kwa-Zulu Natal, South Africa (SA).

Methods: In a retrospective chart review of patients attending Inkosi Albert Luthuli Central Hospital between 2010 to 2020, data on sociodemographic, clinical and antibody profile were extracted using a structured data sheet. Data was analyzed using descriptive statistics, two-sided Fisher's exact tests, Student's t-tests and the Mann-Whitney U test.

Results: Of the 150 patients, 66% were Black African and 29.3% Indian, the mean age was 51 ± 14 years and women made up 80.7%. Diffuse SSc was present in 62%. African patients were significantly younger than Indian patients (47 ± 13 years vs. 56 ± 11 years; p = <0.001), more likely to have diffuse disease (75.3%) and shorter disease duration (median 4 years).

Common clinical features were sclerodactyly (93%), skin induration (91%) and Raynaud's phenomenon (88%). Interstitial lung disease (ILD) (87%) and pulmonary arterial hypertension (PAH) (58%) were significantly more common in diffuse SSc. Anti- nuclear antibodies were present in 97.3%. There was no association between anti-Scl 70 with ILD, nor was there an association between ACA and PAH in this study. There was no ethnic difference in autoantibody profile except that anti-centromere antibodies were not seen in African individuals..

Conclusion: This is the first study to report the differences in presentation of SSc between African and Indian patients in SA. African patients were significantly younger than Indian patients, more likely to have diffuse disease and shorter disease duration.

Key words: systemic sclerosis, clinical features, autoantibodies, South Africa

Introduction

Systemic Sclerosis (SSc) was first described by Carlos in 1752 (1), as a chronic multisystem disease characterized by vasculopathy, fibrosis (2) and autoimmunity (3). The disease is associated with significant disability, disfigurement and a high mortality with 55% of patients dying as a direct consequence of their disease (1, 4). The demographic and clinical features are well described in high income countries and ethnic differences have been observed (5).

In the European Scleroderma Trials and Research (EUSTAR) group studies the mean age of the total cohort was 54.3 ± 13.8 years. Patients with diffuse SSc were significantly younger than those with limited SSc (51.1 vs. 56.6 years, p <0.001). There was a female preponderance with a female to male (F: M) ratio of 6.2:1. The majority of patients were Caucasians (89%), followed by Asians (6.2%) and Africans (2%) (6). In contrast, the recent Genome Research in African American Scleroderma Patients (GRASP) study showed that the African-Americans have a higher incidence of SSc, were younger at age of presentation (42 ± 13.5 years), but had a similar F:M ratio of 5:1. African-American patients also had more diffuse than limited disease and a poorer prognosis compared to Caucasian/European patients (6). In Western India, the mean age was even younger at 35 ± 10.5 years and the F:M ratio higher at 10:1 (7-10). A study from Johannesburg (JHB) in South Africa (SA) in 2018 confirmed a similar mean age at onset (36.1 ± 13 years) and a female preponderance (F:M ratio 7:1) (11). In sub-Saharan Africa (SSA), the mean age at onset in a recent meta-analysis of 91 studies was 36 years (range 4 to 77 years) with a female preponderance of 5.4:1 (12).

Similar to African-American women (8), African patients in SSA, are more likely to have diffuse SSc, which was the commonest presentation in more than 70% of patients (12).

Common clinical manifestations include Raynaud's phenomenon, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Raynaud's phenomenon is the commonest clinical manifestation in all the studies, ranging from 98% in GRASP, 96% in EUSTAR, 82% in JHB, 78% in SSA and lowest 75% in Western India (6, 10, 12-15). The prevalence of ILD varies from 88.2% in Western India to 46 - 52% in the African Americans (16, 17), 30 - 55% in EUSTAR (15), and 40% in JHB (11, 18, 19), and is thought to be more severe in African Americans compared to Caucasians (20). Erzer et

al reported ILD and PAH in 50% and 30% of patients with SSc respectively, (12) and in the JHB study, ILD was the leading cause of death (11, 21). While PAH has been associated with poor outcomes (22-26), newer targeted therapies are associated with improved survival rates (27-30). Scleroderma renal crisis was a rare complication in the EUSTAR (2.1%) (15) and SSA studies (1%) (12) compared to the GRASP study (7%) (6).

Anti-nuclear antibodies (ANA), anti-topoisomerase antibodies (ATA) and anti-centromere antibodies (ACA) were traditionally thought to be associated with specific clinical subtypes of SSc (10, 31, 32), however the EUSTAR studies showed that the autoantibody type contributes more towards systemic complications than the clinical subtype of SSc (8). In the United States of America (USA), ACA was not seen in African Americans. In contrast, Anti-Scl 70 was present in 35% of African Americans compared to 15% of Caucasian Americans (7, 33). In Western India, Anti-Scl 70 was more common in patients with diffuse SSc (7). Erzer et al found the ANA was positive in 65% of patients, which is lower compared to that reported by EUSTAR (93.2%) and anti-Scl 70 and ACA were less common, 12.5% and 9.2% respectively, in SSA (12). In earlier studies from SSA, ACA was not detected in African patients (34, 35), suggesting a possible underlying genetic influence for the expression of the disease and auto-antibodies.

This study aims to add to limited knowledge on SSc from SSA, to describe the clinical, demographic and serological profile of patients with SSc and compare differences in clinical presentation and antibody profile between Black African and Indian patients.

Method

A retrospective descriptive chart review of all patients with a diagnosis of SSc attending the rheumatology clinic at Inkosi Albert Luthuli Central Hospital (IALCH), KwaZulu-Natal (KZN), SA was undertaken. This is the only quaternary hospital in the second largest populated province in SA, providing rheumatology services to the entire province and parts of the Eastern Cape. KwaZulu-Natal has a population of about 10.2 million persons, and Black Africans constitute the majority (87%), followed by Indians 7.4%, Whites 4% and Coloured 1.4% (Census SA 2011). The majority of Indians in SA (58.8%) reside in KZN (Census SA 2011) (36-37).

Patients with SSc were identified from the hospital's electronic data-base. All adult patients (aged 18 years and above) with a confirmed diagnosis of SSc based on clinical and serological features that fulfilled the 2013 American College of Rheumatism/European League against Rheumatism (ACR/EULAR) classification with at least two visits to the clinic were included in the study. Patients with suspected SSc, in whom the diagnosis could not be confirmed and or features of SSc plus any other autoimmune diseases were excluded from the study.

Of the 200 patients identified, 150 patients fulfilled the inclusion criteria and were entered into the study. A structured data collection sheet was used to record demographic data (age, gender, ethnicity, address and income level), and clinical features including type of SSc, disease duration and systemic complications (PAH, ILD, gastrointestinal and renal involvement). Data was extracted from the initial and all subsequent visits. Results of investigations including the antibody results, imaging (X-rays, electrocardiography (ECG), computerized tomography (CT) scans, pulmonary function tests, echocardiography and barium swallow were recorded. Interstitial lung disease was diagnosed on high resolution CT scan of the chest. Pulmonary arterial hypertension was defined as a pulmonary artery pressure more than 25+10 mmHg on echocardiography (34) and GERD was diagnosed either on barium swallow or the presence of characteristic symptoms.

Data analysis

De-identified data recorded by number system were entered into a password protected Research Electronic Data Capture (REDCap) database. IBM SPSS Version 28 was used to analyze the data. Frequency tables with counts and percentages were used to record categorical variables by SSc group (diffuse, limited and sine) and overall. Comparisons were made between limited and diffuse disease types for demographic variables, clinical and antibody profiles and between African and Indian patients. Sine SSc and the other ethnic groups were not compared due to the low numbers. Two-sided Fisher's exact tests were used for categorical variables (ethnicity and sex), and Student T-tests were used for normally distributed numerical variables (age), while the Mann-Whitney U test was used for skewed numerical variables (duration).

Ethical considerations

Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of Kwa-Zulu Natal (BREC/00002785/2021), IALCH, and the KZN provincial department of health. The study was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki and Guidelines for Good Clinical Practice in the Conduct of Clinical Trials with Human Participants in SA (38).

RESULTS

Of the 200 patients identified, 50 patients were excluded because they did not meet the diagnostic criteria for SSc (17 patients), had less than two visits to IALCH rheumatology clinic (12 patients) or had an overlap syndrome (21 patients).

Sociodemographic and disease profile

For the total of 150 patients included in the study, the mean age was 51 ± 14 years. Women made up 80.7% (121 patients) with a F: M ratio of 4.1:1. The majority of patients were either Black African (66%) or Indian (29.3%) (Table 1).

Diffuse disease was present in 62%, limited disease in 35.3% and 2.7% sine SSc. The median duration of disease was 5.7 (IQR 3 -9 years). The majority of patients lived in an urban area and belonged in the lowest economic category (Table 1).

Sclerodactyly (93%) was the commonest clinical manifestation in all patients, followed by skin induration (91%) and the Raynaud's phenomenon (88%) (Table 2).

Patients with diffuse SSc were significantly younger compared to patients with limited disease (49 ± 14 years vs 54 ± 14 years; p = 0.021), and while their disease was of a shorter duration, this did not reach statistical significance (Table 2). Microstomia, myositis, ILD, PAH, pericarditis and a positive anti-Scl-70 antibody were significantly more common in diffuse SSc compared to limited disease (Table 2). In contrast, synovitis recorded in four patients, was only seen in limited disease.

African patients were significantly younger than Indian patients (47 ± 13 years vs. 56 ± 11 years; p = <0.001), and more likely to have diffuse disease and a shorter disease

duration. Microstomia, PAH and pericarditis was significantly more common in African patients compared to Indian patients (Table 3).

Serological profile

The majority of patients were ANA positive (97.3%) and there was no difference in ANA positivity between limited and diffuse SSc (96.2 vs 97.8%). Anti-centromere antibodies were detected in 8% of the total study population, notably none of these were African patients and Anti- Scl 70 was found in 29.3 % of the patients (Table 4). There was no correlation between autoantibodies (ANA, Anti- Scl 70 and ACA) with ILD or PAH (Table 4).

Discussion

This is the first study in almost 20 years to describe the clinical and autoantibody profile of SSc in KZN, SA and the first to compare differences in presentations between African and Indian patients. The mean age of 51 ± 14 years in our study is similar to the EUSTAR study group (54.3 years) (10), but older than that described in African Americans (17), Western India (7), SSA (12) and earlier South African studies in JHB (11) and KZN (35).

The female preponderance reported in this study (F:M ratio of 4:1), is similar to that previously reported in African Americans (5, 17, 39-41), the EUSTAR study) (8), and SSA (5.4:1) review (11, 12), but lower than that reported from India (10:1) (7, 42). The ethnic distribution reflects the KZN population, with the majority of patients being Black Africans (66%). Whilst SSc is known to be less common in Whites (5, 9), the small numbers in this study may possibly be due to a referral bias, with more White patients being treated in the private health care system. The private health care system has a fee based structure and is more accessible to White patients who more commonly have medical insurance and a higher income compared to other ethnic groups (43).

Diffuse SSc was more common in our study, in keeping with studies from Johannesburg and SSA (11, 12). African patients similar to African Americans were more likely to have diffuse SSc (44, 45). Indian patients were more likely to have limited disease, which is in contrast to Western India, where diffuse disease was more common (10).

Whilst Raynaud's phenomenon was slightly less prevalent (88%) in our population compared to 96% in the large EUSTAR study, this was higher than the study in Western

India and the SSA systematic review (12, 15, 21). This might be explained by the fact that Raynaud's phenomenon is sometimes difficult to appreciate in pigmented skin (46).

Interstitial lung disease is one of the commonest complications of SSc especially in diffuse disease. Over 50% of our total population had ILD, which is higher than found in the recent study in Johannesburg (11) but similar to that seen in African Americans, and the EUSTAR group (9-10). Interstitial lung disease was present in 35% of patients with limited SSc and 75% with diffuse SSc (p 0.0001), the latter is higher than the JHB and EUSTAR studies where 52% and 64% of patients with diffuse SSc developed ILD, respectively. In the EUSTAR database ILD developed over time in limited SSc and was associated with anti-Scl 70 positivity, which indicates that patients with anti-Scl 70 positivity should be carefully monitored for lung disease regardless the type of SSc (20). In India ILD was significantly higher in diffuse SSc (88,9%) compared to limited SSc (42.1%) group) (47), comparable to our cohort. There was no statistical difference in the prevalence of ILD between African and Indian patients in our cohort.

Pulmonary arterial hypertension has been associated with poor outcomes. The study frequency of PAH in our cohort was 42% and 27% in African and Indian patients respectively, this is lower than the study in India where 61% of the SSc patients had PAH. Both ILD and PAH remain significant clinical complications (48) and add to morbidity and mortality of the disease (49). Furthermore, ILD and PAH were seen more frequently in our study compared to other SSA studies (12).

Scleroderma renal crisis is a relatively rare manifestation and was reported in 2% and 1% in JHB and SSA, respectively (11, 12). In this study, in this study 2 patients with limited SSc (3.8%) and 2 patients with diffuse SSc (2.2 %) were recorded as having scleroderma renal crisis.

The ANA antibody was positive in the majority of patients (97.3%); higher than the EUSTAR cohort (93.4%), SSA study (87%) and JHB (88.1%), and there was no difference in ANA positivity between patients with limited (96.2%) and diffuse SSc (97.8%). Patients with diffuse disease were more likely to have Anti-Scl 70 antibodies, but this did not correlate with ILD or PHT, nor differed by ethnicity unlike other studies (9, 20). In our cohort ACA antibodies were detected in 8% of the total population similar to the previous JHB (7.5%) (11) but in keeping with previous South African studies, were not detected in

African patients (21, 35, 50). Anti-centromere antibodies were more common in limited disease (7.9%), similar to that previously reported in African Americans in the GRASP study (8%) and lower than previously reported in the EUSTAR study (32.3%) which is dominated by Caucasians (6, 33).

Study limitations

The study was conducted in a single public sector hospital and may not represent all ethnic groups and may have missed patients not referred from lower level hospitals. Due to the retrospective nature of the study, data may be incomplete and not uniformly recorded.

Conclusion

The epidemiology and the clinical presentation of SSc have been extensively studied in developed countries, with local data emerging in the past few years. This is the first study to report the differences in presentation of SSc between African and Indian patients in SA, which is reflective of the KZN population. African patients were significantly younger than Indian patients and more likely to have diffuse disease and a shorter disease duration. Interstitial lung disease and PAH, which are associated with poor outcomes, remain common manifestations, especially in diffuse disease. We confirm the absence of ACA in African patients; the mechanism of which requires further research.

Competing interests

The authors declare that they have no financial or personal relationship that may have inappropriately influenced them in writing this article.

Author's contribution

NS, BC and FP: were involved in the Study concept/ Analysis and interpretation of data/ Drafting manuscript/ Critical revision. All authors read and approved the final version of this manuscript and all contributed to its content

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Results Tables:

Table 1: Baseline characteristics of 150 patients with systemic sclerosis		
		n (%)
Age at diagnosis in years (mean (SD))		51 (14)
Gender	Female	121 (81)
	Male	29 (19)
Ethnicity	African	99 (66)
	Indian	44 (29.3)
	White	3 (2.0)
	Coloured	4 (2.7)
Disease type	Diffuse	93 (62)
	Limited	53 (35.3)
	Sine	4 (2.7)
Disease duration years (median (IQR))		5.7 (3-9)
Residence	Urban	113
	Rural	37
Income level	< R100 000	138
per annum	R100 000 - R350 000	8
	> R350 000	4

Table 2: Comparison of demographic characteristics, clinical features and antibody profile between limited and diffuse systemic sclerosis				
		Limited SSc n=53	Diffuse SSc n=93	p value
Demographic characteristics				
Age in years: (mean (SD))		54.5 (12)	49.1 (14)	0.021
Disease duration in years: (median (IQR))		8 (4- 9.2)	5 (3- 8)	0.06
Female: male ratio		6.6 : 1	3.2 : 1	0.139
Clinical features/organ involvement				
Vascular	Raynaud's phenomenon	49 (92.5)	80 (86.0)	0.244
	Digital ischaemia	17 (32.1)	19 (20.4)	0.116
	Digital ulcers	19 (35)	42 (45)	0.273
	Nail fold capillary changes	19 (35.8)	19 (20.4)	0.075
Skin	Skin induration	47 (88.7)	89 (95.7)	0.170
	Sclerodactyly	48 (90.6)	91 (97.8)	0.099
	Calcinosis cutis	4 (7.5)	6 (6.5)	1.000
	Telangiectasia	20 (37.7)	21 (22.6)	0.070
	Reduced oral aperture	17 (32.1)	67 (72.0)	<0.001
Musculoskeletal	Joint contractures	16 (30)	43 (46)	0.057
	Synovitis	4 (7.5)	0 (0.0)	0.016
	Myositis	2 (3.8)	15 (16.1)	0.040
Gastrointestinal	GERD	31 (58.5)	56 (60.2)	0.838
Respiratory	ILD[1]	15 (28.3)	70 (75.3)	<0.001
Cardiac	PAH[2]	7 (13.2)	48 (51.6)	<0.001
	Pericarditis	0 (0.0)	8 (5.3)	0.003
Renal	Scleroderma renal crisis	2 (3.8)	2 (2.2)	0.760

Antibody profile	Anti- nuclear factor	51 (96.2)	91 (97.8)	0.621
	Anti-Scl 70	9 (17.0)	35 (37.6)	0.014
	ACA	4 (7.9)	3 (3.2)	0.206

ACA- Anti-centromere antibodies, ANA- Antinuclear antibodies, ILD- interstitial lung disease, PAH- pulmonary artery hypertension, Scl-70- serum anti-topoisomerase, SSc – systemic sclerosis, GERD- gastro-esophageal reflux disease

[1]: calculated for 43 and 88 patients with limited and diffuse, respectively in whom information was available

[2]: calculated for 26 and 69 patients with limited and diffuse, respectively in whom information was available

Table 3: Comparison of demographic characteristics, clinical features and antibody profile between Africans and Indian patients with Scleroderma				
		African subjects/ n=99	**Indian subjects/ n=44**	**p value**
Demographic characteristics				
Age in years (mean (SD))		47 (13)	56 (11)	<0.001
Female : male ratio		4:1	3: 1	0.815
Type of disease	Limited	26 (49.1)	25 (47.2)	0.003
	Diffuse	70 (75.3)	18 (19.4)[1]	
	Sine scleroderma	3 (75.0)	1 (25.0)	
Disease duration (median (IQR)) in years		4 (3-8)	8 (5.4- 10)	<0.001
Clinical features/organ involvement				
Vascular	Raynaud's	85 (85.9)	41 (93.2)	0.271
	Digital ischaemia	19 (19.2)	13 (29.5)	0.195
	Digital ulcers	44(44.4)	14 (31.8)	0.197
	Nail fold capillary changes	23 (23.2)	1 3 (29)	0.676
Skin	Skin induration	92 (92.9)	38 (86.4)	0.345
	Sclerodactyly	94 (94.9)	39 (88.6)	0.284
	Calcinosis cutis	7 (7.1)	3 (6.8)	1.000
	Telangiectasia	29 (29.3)	9 (20)	0.691
	Reduced oral aperture	67 (67.7)	15 (34)	<0.001
Musculo-skeletal	Joint contractures	40 (40)	18 (40)	1.000
	Synovitis	2 (2.0)	2 (4.5)	0.587
	Myositis	13 (13.1)	3 (6.8)	0.578
Gastrointestinal	GERD	62 (62)	22 (50)	0.198

Renal	Scleroderma renal crisis	3 (3)	1 (1)	1.000
Respiratory	ILD	62 (62)	21 (47)	0.169
Cardiac	PAH	42 (42)	12 (27)	0.016
	Pericarditis	8 (8.1)	0 (0.0)	0.056
Antibody profile	ANA	96 (97.0)	43 (97.7)	1.000
	Anti-Scl 70	33 (33.3)	10 (22.7)	0.423
	ACA	0	5 (11.4)	<0.001

ACA: Anti-centromere antibodies, ANA: Antinuclear antibodies, ILD: interstitial lung disease, PAH: pulmonary artery hypertension, Scl-70: serum anti-topoisomerase, SSc: systemic sclerosis, GERD- gastro-esophageal reflux disease

Table 4: The correlation of autoantibody profile with pulmonary arterial hypertension and interstitial lung disease in total group

	Pulmonary arterial hypertension				Interstitial lung disease			
	Yes	No	Total	p-value[2]	Yes	No	Total	p-value[3]
	%				%			
ANA positive	98.3	95.0	97.3	0.678	97.7	97.9	97.3	0.754
Anti-Scl positive	32.8	27.5	29.3	0.787	35.6	21.3	29.3	0.149
ACA positive	5.2	10.0	5.3	0.278	4.6	8.5	5.3	0.366

ACA- Anti-centromere antibodies, ANA- Antinuclear antibodies, ILD- interstitial lung disease, PAH-pulmonary artery hypertension, Scl-70- serum anti-topoisomerase.

Appendix 1: Final protocol

The clinical profile, serological profile and management of patients diagnosed with systemic sclerosis in South Africa. A single center experience.

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November 2020

Research topic:

The clinical profile, serological profile and management of patients diagnosed with Systemic Sclerosis in South Africa: a single center experience.

Research question:

What is the clinical and serological profile of SSc in patients treated at IALCH?

Aim of the study:

To describe the clinical and serological profile of SSc in patients at Inkosi Albert Luthuli Central Hospital.

Objectives of the study:

1. To describe the frequency of organ involvement in patients with SSc seen at IALCH.
2. To describe the antibody profile in patients with SSc.
3. To determine the correlation between antibody profile and clinical manifestations.
4. To compare the clinical manifestations and antibody profile in African and Indian patients

1.1 Introduction

Systemic sclerosis, also known as scleroderma, is defined as a complex and clinically heterogeneous disease with protean clinical manifestations, a chronic and frequently progressive course, and significant disability, disfigurement and mortality (1).

SSc is an immune mediated rheumatic disease characterized by fibrosis of the skin, internal organs and vasculopathy. While it can affect every organ (namely the heart, the lungs, kidneys, skin, vascular, musculoskeletal, gastrointestinal tract and the oral cavity), there is marked variability in patterns of skin involvement, organ complications, rates of disease progression, response to treatment and survival (1, 2).

Systemic sclerosis is classified into two major disease subsets based on the extent of skin involvement: limited cutaneous systemic sclerosis which refers restricted skin involvement affecting the limbs distal to the elbows or knees, with or without face and

neck involvement and diffuse systemic sclerosis referring skin involvement proximal to elbows and knees and proximal to metacarpal phalangeal joints (3).

1.2 History of systemic sclerosis

Carlos Curzio first described scleroderma in details in 1752, although scholars believe reference was initially made in writings of this condition from Hippocrates around 400BC. Giovambattista Fontanetti coined the term scleroderma in 1836, but the systemic nature of the disease was only highlighted in 1945 by Robert Goetz, and the term systemic sclerosis was more widely used after that. Swiss artist Paul Klee (1879-1940) was the first famous person who was diagnosed with systemic sclerosis after his death following a five year aggressive disease course (4, 5).

There has been a dramatic improvement in the understanding of systemic sclerosis following Klee's demise although many questions remain. The word scleroderma is derived from the Greek word *skleros*, meaning hard or indurated and *derma* meaning skin, literally thickened skin. Following these publications, more clinicians became aware of the disease and its clinical presentation. Thus, several more cases were reported by the late nineteenth century physicians.(5)

1.3 Epidemiology of systemic sclerosis

Systemic sclerosis is an acquired sporadic disease with a worldwide distribution affecting all races and has a high disease –related morbidity and mortality with an impaired quality of life. Globally around 3-24 per 100 000 persons are estimated to be affected by systemic sclerosis.(6) This small number suggest that the causal factors occur relatively uncommonly and in complex disease, these factors probably include several environmental factors alongside genetic susceptibility.(7)

Systemic sclerosis is more common in women than in men. In developed countries, the ratio of women to men is 3:1 and can be as high as 7 - 8:1. Age between 45 – 64 years, female sex, living in USA and Australia, a positive family history and occupational exposure to silica have been found to be significant risk factors for systemic sclerosis.(8) A wide variation in prevalence has been reported from North America (NA) (13.5 - 44.3

per 100 000 individuals) with a slightly lower rates from Europe (7.2 - 33.9 per 100 1000 individuals) (9). Estimated annual incidence was less than 10 per 100 000 individuals in both Europe (0.6-2.3 per 100 000 individuals) and NA (1.4-5.6 per 100 000 individuals), however an increase in incidence observed over time. The age of diagnosis of SSc is 33.5 - 59.8 years for Europe and 46.1 - 49.1 years in NA, with a male to female ratio of 3.8 - 11.5: 1 and 4.6 - 15:1 respectively(10, 11).

In both Europe and NA systemic sclerosis is more common in non-Europeans when compared to Europeans and in Caucasians compared to South Asians and in NA a higher prevalence has been reported in African American patients (11,(12). Ten -year survival was reported to be 65-73% in Europe and 54-82% in NA, with the cardiorespiratory manifestations, including interstitial lung disease and pulmonary artery hypertension being reported as poor prognostic features (HR range 1.2-6.8).(11)

While other autoimmune conditions like rheumatoid arthritis and SLE have been found that low socioeconomic status and deprivation is associated with increased morbidity and mortality(13, 14), studies from developed countries reveal that there is no association between the incidence and prevalence of SSc and socioeconomic status, and no association between the socioeconomic deprivation and mortality (15).

The recent Genome Research in African American Scleroderma Patients (GRASP) study showed that the African-Americans have a higher incidence of SSc, are younger at age of presentation, have more diffuse disease, a higher prevalence of scleroderma renal crisis and a much poorer prognosis compared to Caucasian/European (16). In Australia, despite advances in therapy and improvements in screening of SSc related complications like PAH in the past few decades, mortality and morbidity in SSc remains high with survival being well below the matched age and gender controls(17).

Poor prognostic features include male gender, diffuse cutaneous subtype, pulmonary arterial hypertension or scleroderma renal crisis and presence of Scl-70 antibody. Cardiopulmonary involvement now supersedes the scleroderma renal crisis as a primary

cause of SS related death while malignancy remains the leading cause of non-SSc related deaths. (7)

There are no epidemiological studies of SSc from India, but several studies have described the clinical and autoantibody profile in small hospital based studies (18). SSc has also been described in human immunodeficiency virus (HIV) infected individuals. The occurrence of both diseases together may have been a coincidence with HIV- associated immune dysregulation providing a conducive environment for the manifestation of SSc in a patient who was probably genetically predisposed(19).

1.4 Clinical manifestations of systemic sclerosis

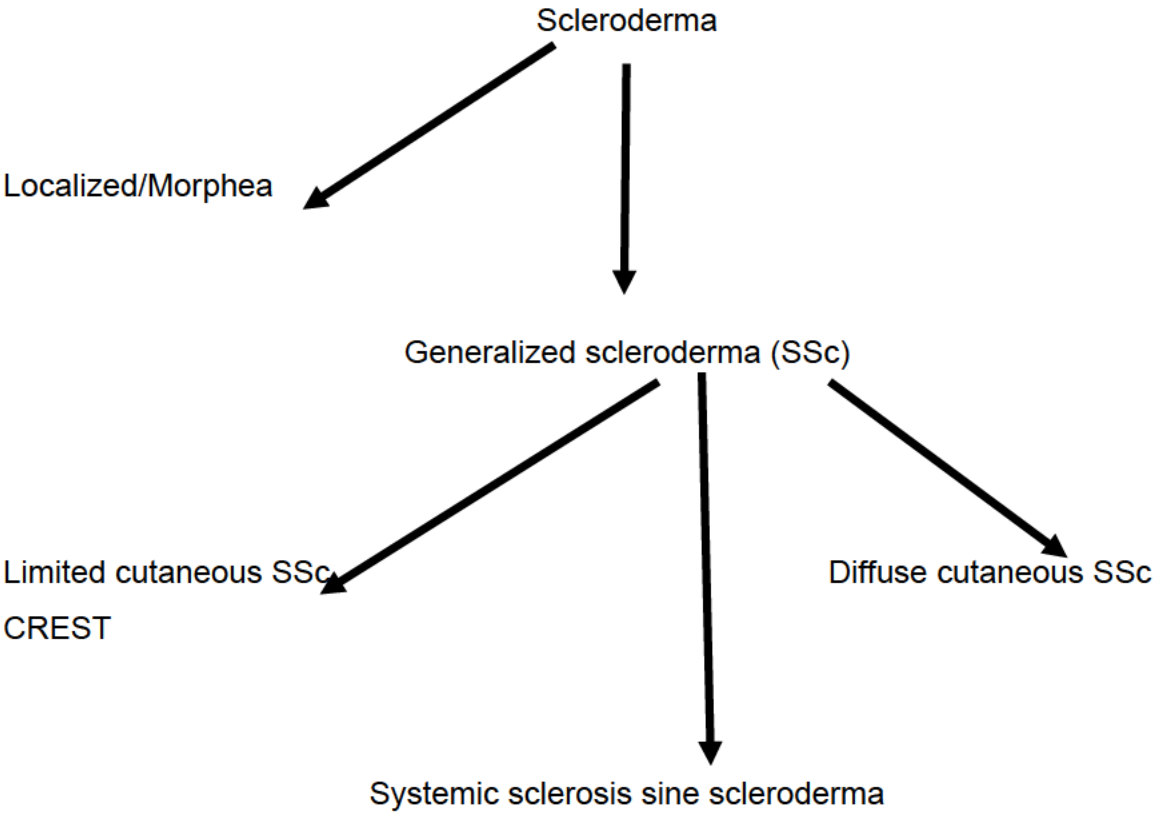
Systemic sclerosis can affect virtually any organ namely the oral cavity, gastrointestinal tract, lungs, the heart, kidneys, skin, vascular system and musculoskeletal system. Although the classification of SSc into diffuse and limited cutaneous subsets is useful, the disease expression is far more complex and multiple distinct phenotypes with unique patterns of manifestations and autoantibodies can be recognized within each subset. Systemic sclerosis may also overlap with other autoimmune disease, most commonly polymyositis (mixed connective tissue diseases), Sjogren's syndrome, autoimmune liver disease or SLE (1, 20)

The two subtypes of SSc differ in terms of skin involvement, clinical and serological profile. In limited cutaneous SSc, Raynaud's phenomenon generally precedes other disease manifestations, usually by years. Limited cutaneous subtype is associated with fibrosis of the skin affecting the acral parts of the body (face and limbs) distal to knees and elbows but proximal to MCPs. Although limited SSc has slow progression of skin fibrosis, it is not limited to skin involvement it is also associated with involvement of esophagus and lungs (21).

Many patients with limited cutaneous SSc display characteristic CREST syndrome (Calcinosis cutis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and mucocutaneous telangiectasia) even though this syndrome is also present in diffuse SSc. Diffuse Systemic Sclerosis is typically associated with diffuse skin induration starting in the fingers (sclerodactyly) and ascending from distal to proximal limbs and the trunk, and

it is associated with early development of interstitial lung disease and renal involvement, which can happen in a short duration or both occur together(22).

Classification of scleroderma



The late and slow organ involvement in limited cutaneous SSc is associated with relatively better prognosis with a 10-year survival of over 90%. Patients with diffuse cutaneous SSc have a poorer prognosis because of a shorter period between the onset of Raynaud's phenomenon and skin symptoms and faster progression of skin and organ disease. In diffuse cutaneous SSc, the 10 year survival ranges between 65-82% which is a result of wide range of systemic complications, the most life threatening of which affect the heart, lungs and kidneys.(23)

Lower limb swelling, and muscle weakness or fatigue might be reported, especially in early stage diffuse cutaneous SSc. Weight loss is often present secondary to a reduced appetite. Multiple organ-based manifestations are a hallmark of SSc and are important in the diagnosis and classification of the disease. In diffuse disease, skin tightness and itching are early features. Occasionally patients present with musculoskeletal pain that

might mimic inflammatory joint disease. Occasionally other regional sensory symptoms are present, such as trigeminal and glossopharyngeal neuralgia or neuropathy(24).

1.4.1 Skin and musculoskeletal involvement

The term scleroderma derives from the most characteristic feature of the disease, skin thickening. The skin thickening is commonly associated with hypo- or hyperpigmentation and telangiectasia. It involves the trunk, extremities, face and neck and results in typical sharp facial features or “mask –like face”. The nasal alar and lips are thinned and radial furrowing around the mouth occurs. In severe cases eyelid movement is limited and the aperture of the mouth is narrowed (microstomia) (25).

In early stages of diffuse cutaneous subtype, the fingers are swollen or puffy, and skin becomes progressively indurated and thin especially on the fingertips where the formation of hard to heal erosions and ulcers may rapidly occur. Skin thickening decreases proximally. Sclerodactyly occur with disease progression limiting the movement of fingers. In limited cutaneous SSc, the progression of disease is slow and Raynaud’s phenomenon usually precedes skin thickening of the face and proximal parts of the extremities. Skin lesions in both subtypes are similar, telangiectasia is more advanced in limited cutaneous SSc whereas hypopigmentation is not as prominent as in diffuse cutaneous subtype. Subcutaneous calcium deposits (calcinosis cutis) are sometimes present in the fingers and more often in limited variant.(26)

Raynaud’s phenomenon is characterized by episodes of reversible vasoconstriction of fingers and toes; it can also affect the tip of the nose or ear lobe. It is triggered by cold temperature, emotional stress or vibration and starts with digital pallor, cyanosis and hyperemia which occurs spontaneously or with rewarming and is the most painful stage in the Raynaud’s phenomenon. If severe can lead to digital ulceration and gangrene(27).

The common musculoskeletal features of SSc include carpal tunnel syndrome, generalized arthralgia and stiffness which are prominent early in the disease and maybe the presenting manifestations (28). Mobility of both small and large joints is progressively impaired and fixed contractures may occur. Synovitis may occur and is an independent

marker of skin progression, and it can be difficult to detect in the presence of puffy hands and swollen joints. Occasionally patients with SSc develop seronegative polyarthritis in the hands, and about 10% have overlap with seropositive rheumatoid arthritis. Muscle weakness is common is SSc and malnutrition, diffuse disuse atrophy and muscle fibrosis maybe contributing factors. In diffuse SSc chronic non-inflammatory is categorized by atrophy and fibrosis may occur with mild elevation in muscle enzymes, but also active inflammatory myositis with proximal muscle weakness may occur with elevated muscle enzymes (29, 30). SSc is the most common connective tissue disease associated with inflammatory myositis and has been discovered in about 42% of individuals with overlap myositis (31).

Gastrointestinal tract involvement is commonest manifestation in SS and occurs in about 90% of individuals and affects all parts of the gastrointestinal tract. Microstomia and xerostomia are common and the esophagus is most frequently involved with about 67% of individuals complaining of dysphagia, odynophagia, regurgitation, chronic cough or hoarseness. The significant alteration of the stomach in SSc results in gastric antral vascular ectasia (GAVE) (23).

Cardiac involvement is often silent and asymptomatic affecting about 10-50% of patients and is more common in diffuse cutaneous SSc (32). It can be primary or secondary to pulmonary arterial hypertension, interstitial lung disease or renal involvement and is a marker of poor outcomes. Pericardial involvement is most common and include pericarditis, pericardial effusions, constrictive pericarditis and rarely cardiac tamponade. Pericardial fibrosis can manifest as heart block (26, 32).

Pulmonary involvement in SSc may be direct or indirect. Direct pulmonary involvement includes interstitial lung disease (ILD) with or without pulmonary arterial hypertension and pulmonary arterial hypertension and less commonly pleural effusions. Indirect pulmonary complications include aspiration pneumonia secondary to esophageal dysmotility, drug toxicity, malignancy, respiratory muscle weakness and restrictive lung defects (33). Interstitial lung disease in SSc has the highest case specific mortality amongst all autoimmune rheumatic diseases (34).

Although ILD is more common in diffuse SSc and pulmonary arterial hypertension to limited cutaneous SSc, any of the pulmonary manifestations may occur in either subset and the rate of progression of ILD is independent of the extent of skin involvement. Pulmonary involvement also may occur in SSc without cutaneous involvement, an entity called scleroderma sine scleroderma, in which the diagnosis is suggested by the presence of telangiectasia, Raynaud's phenomenon and positive antinuclear antibody tests. Interstitial lung disease and pulmonary arterial hypertension have both been shown to be more frequent and more severe in African Americans compared to Caucasians (35).

In a study of 63 African patients with SSc in Johannesburg SA, pulmonary fibrosis was found in 56% of the patients (36). In a subsequent study from the same center, ILD was reported in 40% of patients. Predictors of ILD included disease duration and diffuse skin involvement (37). Pulmonary disease was the leading cause of death in these patients. The limitations of the study included the relatively small size and lack of right heart catheterization to confirm pulmonary artery hypertension (37). In Africa however, pulmonary arterial hypertension has been previously reported in 7.4% of 202 patients with scleroderma (38). While pulmonary arterial hypertension has been associated with a poor outcomes, newer targeted therapy is associated with improved survival (39).

Renal involvement affects 10% of individuals with SSc and is often a life-threatening manifestation of SSc and is more commonly seen in diffuse SSc. Renal involvement occurs usually early in the disease and includes malignant hypertension in about 75% of the cases, renal dysfunction, and oliguria (37)). Scleroderma renal crisis is a serious complication and results from a vasculopathy of small vessels resulting in intimal proliferation of the vascular lumen and decrease in renal blood flow (40). Risk factors for renal crisis are Black race, male sex, diffuse cutaneous manifestations and the use of high dose corticosteroids. The survival rate has improved dramatically with the development of ACE inhibitors but the death rate remains high (41).

Neurological involvement is rare and include headaches, epilepsy and cognitive disorders. Patients present with peripheral neuromuscular disorder i.e. myopathy, trigeminal nerve disorder, motor and sensory neuropathy and carpal tunnel syndrome. Depression and anxiety have also been reported as secondary to the disease (42).

There appears to be a higher prevalence of malignancy in SSc especially in men and with diffuse cutaneous involvement. Systemic sclerosis is thought to be an independent risk factor for lung and breast cancer; however, the exact etiology of this increased risk is unknown. Lung cancer and oesophageal adenocarcinoma typically occur in the setting of long-standing interstitial lung disease and gastro-esophageal reflux disease. In contrast the breast and ovarian cancer and lymphomas tend to occur in close temporal association with SSc.(43)

Table: A Comparison of Organ System Involvement in Diffuse and Limited Systemic Sclerosis

Organ system involvement	Diffuse%	Limited %
Skin thickening	100	95
Telangiectasia	30	80
Calcinosis	5	45
Raynaud's phenomenon	85 to 95	95
Arthralgias or arthritis	80	60
Tendon friction rubs	65	5
Myopathy	20	10
Esophageal hypomotility	75	75
Pulmonary fibrosis	35 to 59	25 to 35
Congestive heart failure	10	1
Renal crisis	15	1

1.5 Serological profile of SSc

Several autoantibodies are associated with SSc. These include anti-centromere, anti-topoisomerase1 (Scl-70), anti-RNA polymerase III (ARA), anti-fibrillarin (U3-RNP), antiTh/To, and anti-platelet derived growth factor receptor alpha (anti-PDGFR) antibodies (1). Antinuclear antibodies (ANA) are present in more than 90% of patients with SSc. Specific serological profiles correlate with patterns of clinical presentation and prognosis in SSc. The presence of anti- centromere antibodies (ACA) is associated with pulmonary arterial hypertension, anti- topoisomerase 1 antibodies (ATA) associated with ILD and

anti- RNA polymerase III antibodies associated with renal crisis. Anti-centromere antibodies (ACA) and ATA are mutually exclusive in SSc and the concomitant expression of both antibodies is extremely rare(44).

Table: Clinical and antibody profiles of diffuse and limited systemic sclerosis:

	ACA	Th/To	U1-RNP (MCTD)	Pm-Scl	U3-RNP Fibrillarin	Scl-70 Topoisomerase I	RNA Pol3
SSc subset % of patients	Limited 50-90%	Limited 4-16%	Limited 100%MCTD	Limited 3%	Diffuse 7%	Diffuse 20-30%	Diffuse 25%
Lungs	PAH	ILD +PAH	PAH	ILD Myositis	ILD+PAH	ILD	-
Kidneys	-	-	-	-	-	SRC	SRC

Adapted from Sten VD, Lucas Ferringet al. PAH and severe Pulmonary fibrosis in SSc Patients with nuclear antibody, J Rheumatol 34:2230

Anti-centromere antibodies maybe found in the serum of SSc patients years before the disease clinically manifests and continue to be expressed throughout the course of the disease (45). Patients with Raynaud's phenomenon who also expresses ACA are at higher risk of developing SS compared to those patients who have Raynaud's phenomenon without ACA. Moreover, ACA are specific for SSc and rarely found in other autoimmune diseases or in healthy individuals (46).

The frequency of autoantibodies differs between African Americans and Caucasians, with anti- topoisomerase1 and anti- fibrillarin (anti-U3 and U1 RNP) more frequent in African Americans whereas in Caucasians the anti-centromere antibodies, anti-RNA polymerase III and anti-topoisomerase1 were more frequent (37) (Ashmore et. al., 2018). Recent studies demonstrated a strong association between anti- fibrillarin antibodies and HLADRB1 *8:04. these genetic influences could be important factors contributing to differences in disease outcome.(47)

In the European Scleroderma Trial and Research group (EUSTAR) the status of autoantibodies contributed more towards systemic complications than the clinical subtype of SS. The prevalence of ARA antibodies was found to be two-fold higher in a Brazilian study indicating the severity of the disease in their population group. The assessment of patients from a tertiary center might have contributed to the selection of more severe cases. The study done in Brazil confirmed the findings of the studies done previously in developed countries, and ACA antibody was associated with indicators of better prognosis, differently from ATA-1 antibody associated with diffuse SSc and higher severity(48).

SSc diagnostic classification

The ACR classification criteria 1980 was revised because it lacked sensitivity, especially in individuals with limited SSc or early disease. 2013 ACR/EULAR criteria is superior and more sensitive, it is more inclusive helps with early disease diagnosis (</= 3 years since diagnosis (49, 50).

The sensitivity and specificity have been found to be 91% and 92% respectively for new criteria and 75% and 72% for the old criteria. This has allowed in addition to those diagnosed using old criteria several additional cases diagnosed with SSc using new criteria(51).

1980 ACR classification criteria (old criteria) ACR preliminary classification of systemic sclerosis

Diagnosis = 1 Major criterion or 2 minor criteria

Major criterion: Proximal scleroderma

Minor criteria

Sclerodactyly

Digital pitting or scars or loss of substance from finger pad

Bibasilar pulmonary fibrosis

2013 ACR/ EULAR criteria for the classification of systemic sclerosis (scleroderma)

Item	Sub- item(s)	Weight/ score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count higher score)	Puffy fingers	2
Fingertip lesions(only count the higher score)	Digital tip ulcers	3
Telangiectasia	-	2
Abnormal nail fold capillaries	-	2
Raynaud's phenomenon	-	2
PAH and/or ILD (maximum score is 2)	PAH or ILD	2
Systemic sclerosis related autoantibodies (anti-centromere, anti-topoisomerase I (anti-Scl-70), anti-RNA polymerase III (maximum score is 3)	Anti-centromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3

*The criteria are not applicable to patient with skin thickening sparing the fingers or to patients or to patients who have scleroderma like disorder that better explains their manifestations (e.g. nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleroderma diabeticorum, scleromyxoedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic athropathy).

The total score is determined by adding the maximum weight (score) in each category. Patients a total score of >/=9 are classified as having definite scleroderma.

1.6 Management and challenges in systemic sclerosis

Management of SSc includes early diagnosis of the disease, early diagnosis of organ involvement and early recognition of those at risk for development of new organ complications (52). Currently there is no single cure for SSc, the clinical presentation varies between individuals and the current management is individualized based on individual's clinical presentation, extent of organ involvement and availability of resources. Symptomatic treatment has shown to improve patient's quality of life. Immunosuppressive drugs aims at inhibiting tissue fibrosis, vascular and immune system alterations which the main components of disease pathogenesis, such as azathioprine, methotrexate, cyclophosphamide, rituximab and mycophenolate mofetil and has been the main stay for the treatment of fibrotic complications like interstitial lung disease (53).

Skin involvement and Raynaud's phenomenon:

D-Penicillamine, bovine collagen, methotrexate, mycophenolate mofetil and allogenic bone marrow transplantation have demonstrated benefit in treatment of skin induration and fibrosis in SSc(54). Moisturizers, histamine ½ blockers, tricyclic antidepressants and trazodone have been used as treatment measures for prutitis (55).

Raynaud's phenomenon have been treated with calcium channel blockers, prazocin, prostaglandin derivatives, dipyridamole, aspirin and topical nitrates(56, 57).

Gastrointestinal involvement:

For gastrointestinal complications treatment is mainly symptomatic, for intestinal bacterial overgrowth broad spectrum antibiotics have been used, for oesophageal reflux symptoms the proton pump inhibitors, and for gastric antral vascular ectasia cauterization or laser probe therapy is used. High fiber diet and laxatives are recommended for constipation(58). Antacids, histamine blockers, reflux and aspiration precautions, octreotide, stool softeners and laxatives have been used for the treatment of gastrointestinal symptoms in SSc(59, 60).

Dysphagia is very common in patients with SSc or inflammatory myopathies and its management include rehabilitation measures, corticosteroids, immunosuppressive agents and rarely surgical measures such as cricopharyngeal myotomies and dilatation(34).

Lung involvement: Mycophenolate mofetil, Methotrexate, Cyclophosphamide, Rituximab have shown success in the treatment of pulmonary fibrosis/ alveolitis. Nintedanib is a tyrosine kinase inhibitor which targets growth factors like fibroblast growth factor receptor and others, has been approved by FDA in September 2019 and has been shown to improve pulmonary function in SSc individuals with interstitial lung disease(61). In addition to immunosuppressive therapies, N-acetylecisteine has been shown to significantly improve outcome when added to standard treatment with Azathioprine and oral steroids(62).

Pulmonary arterial hypertension: General management involves the use of diuretics, anticoagulation, oxygen and digoxin for the treatment of heart failure (63, 64).

Prostaglandin derivatives like iloprost, phosphodiesterase type 5 inhibitors like sildenafil and endothelin receptor antagonists such as ambricentan have been used to treat PAH. Combination therapy has been shown to be have better outcomes than monotherapy and the American College of Chest Physicians and European Society of Cardiology recommend the use of combination therapy, in individuals unresponsive to monotherapy, as it reduces the risk of disease progression and improves effort tolerance. (63)

Table: Modified Rodnan Skin Scoring (MRSS) (65)

	Right :0/1/2/3	Left: 0/1/2/3
Fingers		
Hands		
Forearms		
Upper arms		
Face		
Anterior chest		
Abdomen		
Thighs		
Legs		
Feet		
Total		

0- no thickness 1-mild thickness 2-moderate thickness 3severe thickness

Table: immunosuppressive therapy of systemic sclerosis

Systemic sclerosis complications	**Immunosuppressive agents**
Active skin involvement	Mycophenolate mofetil Methotrexate Cyclophosphamide Rituximab Intravenous immunoglobulin
Pulmonary fibrosis	Mycophenolate mofetil Methotrexate Cyclophosphamide Rituximab
Cardiac scleroderma	Mycophenolate mofetil Cyclophosphamide
Renal crisis	Low dose Mycophenolate mofetil

1.7 Systemic sclerosis in Africa

There have been no formal epidemiological studies of SS in Africa and SS is thought to be uncommon. In Egypt the pattern of clinical presentation in patients with SSc according to 1980 classification criteria of the American College of Rheumatology (ACR), namely, the presence of one major criteria or two or more minor criteria and patients with skin thickening sparing the fingers were excluded, was described. (66).

In a further study in which patients with SSc were selected according to the 2013 ACR/European League Against Rheumatism (EULAR) SSc classification criteria, 16% of patients with SS were males and 84% were females, giving the male: female ratio of 1:5.25.(66-68) .

A Nigerian study found SSc represented 1.1% of all the patients seen in a rheumatology clinic suggesting that this was a rare disease (58). However, it was a possibility that this was an under-estimation as some patients were likely to have been managed in the dermatology clinic. In the small number of patients, there was a higher incidence of diffuse cutaneous SSc, which was present in 8 out of 14 cases and limited cutaneous subtype being present in 3 out of 14 cases. The female preponderance seen in SSc was confirmed together with early age of presentation among Blacks with a mean age of 40.3 years. Further confirmation of the rarity of SSc in Africa, is the case report of SSc in 48-year-old Liberian woman. The presentation confirmed the findings previously studied in developed countries(69).

SSc is not rare in sub-Saharan countries, however the clinical presentation differs when compared to Caucasians in that there is an increased prevalence of anti-fibrillarin autoantibodies and increased frequency of diffuse skin involvement and focal skin hypopigmentation(47, 70) .

1.8 Systemic sclerosis in South Africa

Similarly, there have been no epidemiological studies on the incidence and prevalence of SSc in SA. The limited studies describe the spectrum of clinical manifestations and antibody profile in South African subjects. In an early study, progressive SSc was described in South African gold miners exposed to silica. Similar to other South African studies, anti-centromere antibodies were not seen in African subjects (71). An

association between progressive SSc and cumulative silica dust dose to onset of SSc was reported. However, less than half of the cases of progressive SSc fact contracted silicosis(27).

Subsequently, in a study from Johannesburg in a retrospective study of SSc in 63 African patients with SSc, there was a female preponderance with a female to male ratio of 4.6:1. The mean age of onset at 36.1 years was lower than that of developed countries. An exposure to silica was present in four of the 11 males and in nine women (36). In a more recent study in which the majority of patients were Africans, 40% of the subjects has interstitial lung disease (ILD) which was also the leading cause of death.(37)

Systemic sclerosis sine scleroderma presents with typical organ involvement but with no clinical evidence of skin thickening. It is characterized by vascular abnormalities, fibrosis, inflammation and atrophy of the skin and internal organs. This subset is more likely to be associated with systemic involvement such as renal crisis, pulmonary fibrosis and cardiomyopathy (Dire: 2015).

2.5 Methodology

2.5.1 Rational for the study

There are limited studies of systemic sclerosis in South Africa. To date the studies have largely described the clinical manifestations and antibody profile in African patients. The last study done in Durban in 1991. Since then, there have been advances in serological and imaging investigations and therapeutics. The recent studies are predominantly from JHB and differences in presentations and Indian population

Inkosi Albert Luthuli Central Hospital (IALCH) is a quaternary hospital and serves as a referral hospital for KwaZulu-Natal and part of the Eastern Cape. The Rheumatology Department provides an outpatient and inpatient service for patients with systemic sclerosis. Given the demography of the province, the majority of patients attending the clinic are Indian and African subjects.

2.5.2 Study design

In this study a retrospective chart review will be undertaken of the electronic records of all patients with SSc attending the rheumatology clinic at Inkosi Albert Luthuli Central Hospital (IALCH).

2.5.3 Study location

The study will be conducted in Durban which is located in eThekwini district which is the largest district in KZN. The Metro area has a population of about 3.8 million, over 51%of residents are black, nearly one quarter of the population is Indian or Asian, while 15.3% are white and 8.6% are designated as colored. (2007bConsensus Stats SA).

2.5.4 Study population:

All patients with SSc attending IALCH Rheumatology clinic for the past 10years will be recruited. The study will include both male and female gender and all races. How will you identify patients: say you will use ICD codes (relevant codes) and all patients with a diagnosis of Scleroderma?

2.5.5 Sample size: A convenience sample of all patients identified with a confirmed diagnosis of SSc, the study will look at all files of individuals with SSc for the past 10years.

2.6. Inclusion criteria

-A confirmed diagnosis of SSc based on clinical and serological features.
-At least two visits to the clinic.

2.7 Exclusion criteria

-Patients with suspected SSc in whom the diagnosis cannot be confirmed on clinical and serological features
-Patients with features of SSc plus any other autoimmune diseases such as mixed connective tissue disease.

2.8 Methods:

Patients with SSc will be identified from the clinic and hospital records using ICD 10 codes. Data will be extracted from the electronic case records using a structured data sheet. The study will look at the following information: Demographic, Clinical, Comorbidities, HIV, Serology, Drug treatment, lung function, CXR, Echo.

2.9 Data collection

Data collection sheet will be used.

2.10 Data analysis

The IBM SPSS19 version 21 Microsoft excel computer program will be used to analyze the data collected from the questionnaires. Using this type of program, it gives the researcher the opportunity to analyze and interpret data from different approaches, through using this software the researcher will be able to analyze collected data through graphs and tables. The significance of all tests will be set at $p<0.05$, in cases where frequencies maybe small the exact test will be used to determine the p value.

2.11 Reliability and validity

Reliability: a structured data extraction will be used to achieve reliability.

Validity: all patients in whom a diagnosis of SS based on ACR diagnostic criteria is confirmed to achieve validity.

2.12 Limitations to the study

The sample will be taken in a public sector hospital, thus the representation of different ethnic groups may be affected, because the sample may over represent the subjects from lower socio-economic groups who are only dependent on the public sector health system. Due to the retrospective nature of the study, data may be incomplete and not uniformly recorded.

2.13 Ethical considerations

All participants' details will be kept confidential and their clinical details will be de-identified and collected on a data sheet, with a code known only to the principal researcher. The

data will also only be stored on a password protected source. There will be no patient contact.

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Appendix 2: Guidelines for Authorship: International Journal of Rheumatology Journal of manuscript Submission

Submission of manuscript implies: the original, unpublished investigative reports regarding clinical, laboratory, and translational aspects of rheumatology. The publication has been approved by all authors and the publisher will not be held legally responsible should there be any claims for compensation.

- Abstract: maximum of 250 words (Objective, Methods, Results, and Conclusion)
- Word count: maximum of 3500 for full-length articles (from Introduction through Discussion)
- Tables and figures: maximum of 6, combined
- References: maximum of 50 for full-length articles

Organize manuscripts to include the following sections:

- Title Page
- Abstract
- Introduction
- Methods
- Results
- Discussion
- Acknowledgment if applicable
- References
- Figure Legends
- Tables and Figures
- Data Supplements
- Appendix **(Non-author collaborator list only)**

Cover Letter

Manuscripts should be accompanied by a cover letter indicating that the final manuscript has been seen and approved by all the authors that they have obtained the required ethical approvals, that they have given necessary attention to ensure the

integrity of the work, and that they agree to bear the applicable publication charges if their manuscript is accepted for publication

Manuscripts, tables, figures, data supplements, and appendix should be submitted as separate files.

Details of Format and Organization

Title Page

- Short running head (maximum of 30 characters)
- Full title of manuscript (maximum of 20 words)
- Complete given names and surnames of all authors with ORCID ID if any for author byline
- Source(s) of support in the form of grants or industrial support
- Initials, surnames, appointments, and highest academic degrees of all authors (e.g., MD, PhD), and affiliated department(s) and institution(s)
- Conflict of interest
- Corresponding author's name, address, and email
- Key Indexing Terms -maximum of 6
- Title Page Templates are available for the following:

Abstract

- Full-length manuscripts (250 words)
- Briefly describing Objective, Methods, Results, and Conclusion.

Acknowledgment

- Acknowledgment, if applicable, should be added after the Discussion of the paper and before the references.
- It should not acknowledge grant or industrial support for fellowship awards, all of which should appear on the title page.

References

- Authors are responsible for the accuracy of references, which must be verified against original sources in the manuscript and on the page proof.
- Number references consecutively in the order in which they are mentioned in the text.
- Identify references in text, tables, and legends by Arabic numerals (in parentheses).
- For references cited only in tables or figure legends, number references consecutively in the order in which they appear in the text.

Appendix 3: Ethics

Department of Health Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202107_026

Dear Dr S. Shandu
(UKZN)

Approval of research

1. The research proposal titled **'The clinical profile, serological profile and management of patients diagnosed with Systemic Sclerosis in South Africa: a single center experience'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   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. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *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.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

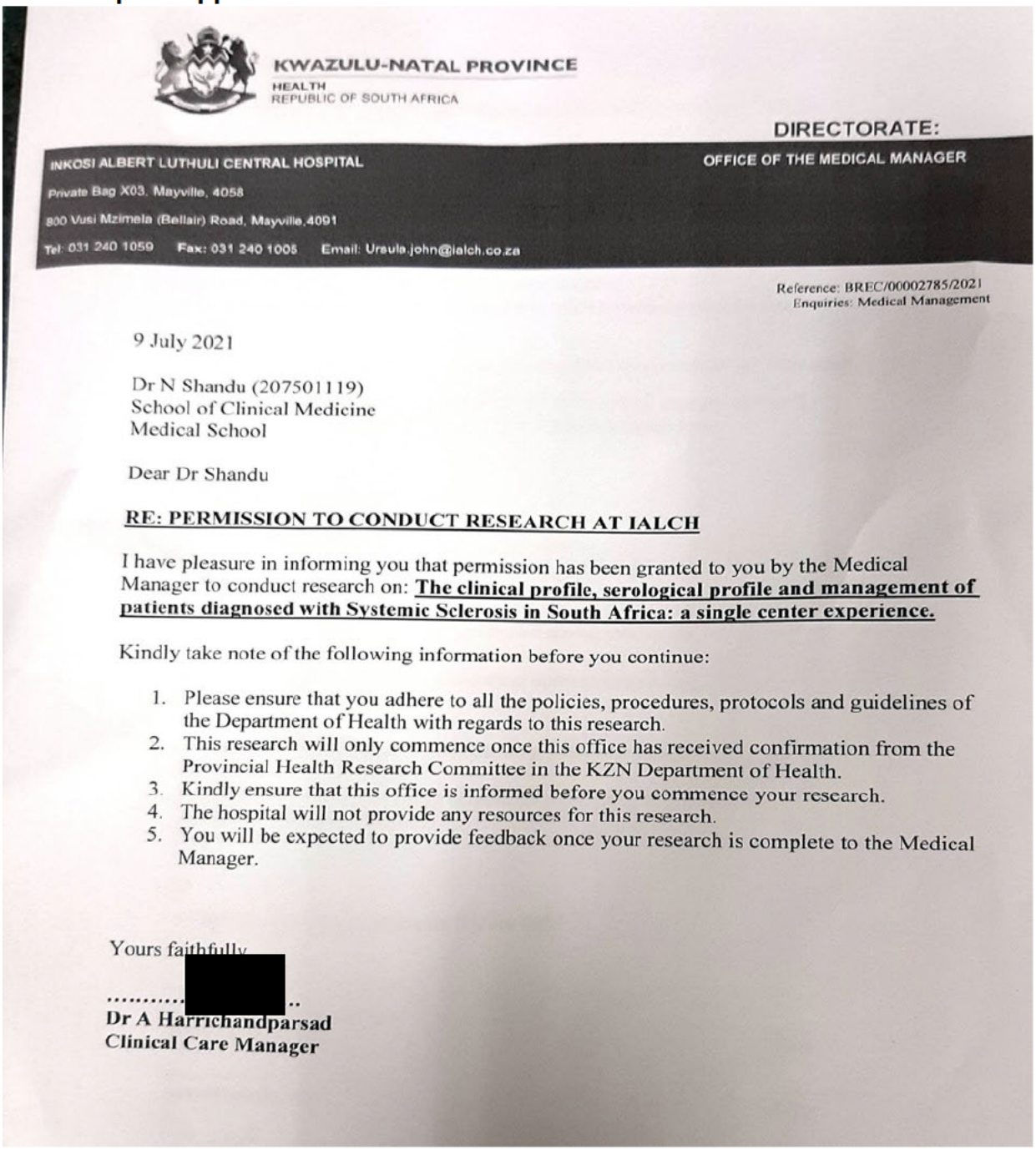
For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 11/08/2021

KZN Hospital Approval



KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
OFFICE OF THE MEDICAL MANAGER

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

Reference: BREC/00002785/2021
Enquiries: Medical Management

9 July 2021

Dr N Shandu (207501119)
School of Clinical Medicine
Medical School

Dear Dr Shandu

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The clinical profile, serological profile and management of patients diagnosed with Systemic Sclerosis in South Africa: a single center experience.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....[redacted]..
Dr A Harrichandparsad
Clinical Care Manager

BREC ethics certificate

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YA KWAZULU-NATALI

21 August 2021

Dr Nokwazi Shandu (207501119)
School of Clinical Medicine
Medical School

Dear Dr Shandu,

Protocol reference number: BREC/00002785/2021
Project title: The clinical profile, serological profile and management of patients diagnosed with Systemic Sclerosis in South Africa: A single center experience
Degree: MMed

EXPEDITED APPLICATION: APPROVAL LETTER

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

The conditions have been met and the study is given full ethics approval and may begin as from 21 August 2021. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Amended_Lockdown_Level_3_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 21 August 2021. 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 (2020) (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 14 September 2021.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

Appendix 4: Data collection sheet

DATA COLLECTION SHEET		
PATIENTS DETAILS		
Unique identifier		
Ethnicity	1=African 2=Indian 3=Coloured 4=White	
Age		
Sex	1=Male 2=Female	
Age of onset		
PRESENTING FEATURES		
Vascular :		
Raynaud's phenomenon	1=Yes 2=No	
Digital ischaemia	1=Yes 2=No	
Ulcers	1=Yes 2=No	
Capillary changes in the nail beds	1 =Yes 2=No	
Gangrene	1=Yes 2=No	
Sclerodactyly	1=Yes 2=No	
Skin:		
Induration	1=Yes 2=No	
Calcinosis cutis	1=Yes 2=No	
Telangiectasia	1=Yes 2=No	
Hyperpigmentation	1=Yes 2=No	
Xerosis	1=Yes 2=No	
Pruritis	1=Yes 2=No	
Oral:		
Xerostomia	1=Yes 2=No	
Reduced aperture	1=Yes 2=No	
Mucocutaneous telangiectasia	1=Yes 2=No	
Musculoskeletal:		
Fatigue	1=Yes 2=No	
Myalgia	1=Yes 2=No	
Arthralgia	1=Yes 2=No	
Joint contractures	1=Yes 2=No	
Tendon friction rubs	1=Yes 2=No	
Myositis	1=Yes 2=No	
Upper GI:		
GERD	1=Yes 2=No	
GAVE	1=Yes 2=No	
Barrett's	1=Yes 2=No	
Gastroparesis	1=Yes 2=No	
Lower GI:		
Hypomotility	1=Yes 2=No	
Bacterial overgrowth	1=Yes 2=No	
Pseudo obstruction	1=Yes 2=No	
PULMONARY:		
Dyspnoea	1=Yes 2=No	

ILD	1=Yes 2=No	
PAH	1=Yes 2=No	
Cardiac:		
Pericarditis	1=Yes 2=No	
Diastolic dysfunction	1=Yes 2=No	
Cardiomyopathy	1=Yes 2=No	
Arrhythmia	1=Yes 2=No	
Renal:		
Proteinuria	1=Yes 2=No	
Oliguria	1=Yes 2=No	
Renal failure	1=Yes 2=No	
MHAT microangiopathic hemolysis anemia and thrombocytopenia		
Scleroderma renal crisis	1=Yes 2=No	

Hypertension	1=Yes 2=No	
CNS:		
Peripheral neuropathy	1=Yes 2=No	
Encephalopathy	1=Yes 2=No	
Psychosis	1=Yes 2=No	
Seizures	1=Yes 2=No	
TIA	1=Yes 2=No	
Anxiety disorder	1=Yes 2=No	
Optic neuropathy	1=Yes 2=No	
UNINE ANALYSIS		
Proteinuria	1=Yes 2=No	
Cellular Casts	1=Yes 2=No	

Laboratory Testing:				
FBC				
WCC				
HB				
MCV				
MCH				
Platelets				
U&E:				
NA				
K				
CL				
HCO3				
AG				
UREA				
CREATININE				
LFT:				
Total protein				
Albumin				
Bilirubin				

ALT					
ALP					
GGT					
Other:					
RF					
CK					
Fe					
ANTIBODIES:					
ANA	1=Positive 2=Negative				
Anti-SL-70	1=Positive 2=Negative				
ACA	1=Positive 2=Negative				
Anti –RNA Polymerase III	1=Positive 2=Negative				
ANTI-CCP	1=Positive 2=Negative				
Anti DS DNA	1=Positive 2=Negative				
Anti-SM	1=Positive 2=Negative				
RNP antibodies	1=Positive 2=Negative				
PULMONARY FUNCTION TEST:					
Restrictive ventilatory defect:	1=detected 2=not detected				
FEV					
FEV1					
CXR	1=Done 2=Not done				
Interstitial pulmonary changes:	1=Yes 2=No				
ECG	1=Done 2=Not done				
ECHO	1=Done 2=Not done				
PHT	1=Yes 2=No				
PAS Value					
EF					

HRCT	1=Done 2=Not done	
ILD	1=Yes 2=No	
Other investigations		
DIAGNOSIS		
Limited cutaneous	1=Yes 2=No	
Diffuse	1=Yes 2=No	
Sine scleroderma	1=Yes 2=No	
Risk factors:		
Family history of A/I Disorders	1=Yes 2=No	
Environmental exposure:	1=Yes 2=No	
Silica dust exposure	1=Yes 2=No	
Mine worker	1=Yes 2=No	
Petroleum –based products	1=Yes 2=No	
Pesticides	1=Yes 2=No	
Drugs:		
Bleomycin	1=Yes 2=No	

Carbidopa	1=Yes 2=No	
Cocaine	1=Yes 2=No	

Treatment : Medication	Y/N		duration	
Cyclophosphamide				
MMF (mycophenolate mofetil)				
PPI				
Methotrexate				
ACE-I inhibitors				
CCB (calcium channel blockers)				
Phosphodiesterase 5 inhibitor				
Dialysis				
Low dose steroids				
NSAIDS				