COMORBIDITIES IN SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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

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Declaration

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

The 9th day of February, 2017

Dedication

To my wonderful family

for their support and understanding.

Presentations arising from this work

1. Greenstein L, Tikly M, Makan K. Comorbidities in South Africans with Systemic Lupus Erythematosus. Poster presentation. Wits Health Research Day. September 2015.
2. Greenstein L, Tikly M, Makan K. Comorbidities in South Africans with Systemic Lupus Erythematosus. Oral presentation. 10th European Lupus Meeting, Venice. October 2016

Abstract

Introduction:

Systemic lupus erythematosus (SLE) is a rare multisystem autoimmune disease which occurs most severely in young females of African descent. Life expectancy is reduced, either directly due to the disease itself or related comorbidities.

Aim of study:

To determine the prevalence and spectrum of comorbidities in patients with SLE attending the Chris Hani Baragwanath Academic Hospital (CHBAH) Lupus Clinic.

Patients and Methods:

A retrospective record review of 200 SLE patients attending the CHBAH Lupus Clinic for at least 6 months. Data collected included demographics, clinical and serological evidence of SLE, autoantibody status, treatment modalities and comorbid conditions. The Charlson Comorbidity Index was used to measure the total comorbidity burden.

Results:

The majority of patients were black females (94%) with a mean age (SD) of 34.6 years (11). Disease duration and American College of Rheumatology (ACR) criteria fulfilled were 7 years and 5 respectively. The median (IQ range) CCI was 1 (0-3). Baseline and cumulative prevalence of one or more comorbidities was 36.5% (95% CI: 29.8-43.6%), and 56.0% (95% CI: 48.8-63.0%), respectively. The most frequent comorbidities were hypertension (HPT) (43.5%), severe infections (29%), tuberculosis (TB) (15%), and HIV infection (9%). Univariate risk factors for serious infection were the number of ACR criteria fulfilled and leucopaenia, while both

univariate and multivariate risk factors were anti-Sm antibodies, thrombocytopaenia and the use of immunosuppressive drugs. Risk factors for HPT included age at onset, disease duration, CNS involvement and chloroquine use. Risk factors for TB were disease duration and the use of azathioprine. Protective factors were age of onset, arthritis as a clinical criteria and hypocomplementaemia.

Conclusion:

In this study of predominantly black females, comorbidities were common but the spectrum differs to those reported in industrialised, Western countries. Infections, both those requiring hospitalisation for intravenous antibiotics, and TB, were amongst the commonest comorbidities, relating to risk factors such as the use of immunosuppressive drugs, autoantibody status and disease duration. Furthermore, despite the high prevalence of HPT, cardiovascular comorbidities were very rare.

Acknowledgements

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List of Abbreviations

ACR	American College of Rheumatology
ANA	Anti-Nuclear Antibody
APS	Anti phospholipid syndrome
AVN	Avascular necrosis
BMD	Bone mineral density
C3	Complement component 3
C4	Complement component 4
CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
CCF	Congestive cardiac failure
CHBAH	Chris Hani Baragwanath Academic Hospital
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CS	Corticosteroids
CTD	Connective tissue disease
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DM	Type 2 diabetes mellitus

ESRD	End stage renal disease
HIV	Human immunodeficiency virus
HPT	Hypertension
LA	Lupus anticoagulant
LN	Lupus nephritis
MetS	Metabolic syndrome
MI	Myocardial infarction
MMF	Mycophenolate mofetil
OP	Osteoporosis
PUD	Peptic ulcer disease
PVD	Peripheral vascular disease
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TB	Tuberculosis
WR	Wasserman reaction

Chapter 1:

1.1 Introduction

Systemic lupus erythematosus (SLE) is a rare multisystem autoimmune disease, occurring most commonly and severely in young females of African descent in the South African setting. (Tikly and Navarra, 2008). It results from a multifactorial interplay between genetics and the environment (Tikly and Navarra, 2008).

"*I have lupus, but lupus doesn't have me*." This simple statement by Nick Cannon, an entertainer and television celebrity suffering from this disease, highlights how easily one can be defined by having lupus.

The word lupus means wolf in Latin. Rogerius, an Italian physician, likened the erosive facial features of lupus sufferers to wounds from a wolf bite. Superstition prevailed in the Middle Ages and at this time, patients with lupus were associated with wolves because of their disfiguring disease (Mallavarapu and Grimsley, 2007).

Three periods define the history of lupus – the classical, neoclassical and modern. During the classical period, lupus was considered purely a disorder of the skin. Original descriptions by Bateman and Willan, are now recognisable as lupus vulgaris, an ulcerative rash attributed to tuberculosis (TB), a disease that was rife during this period; but it was Biett and Cazenave who coined the term lupus erythematosus and described the typical discoid lupus rash. Around the same time, Kaposi and his father-in-law, Ferdinand von Hebra, described the well-known butterfly malar rash

(Mallavarapu and Grimsley, 2007). Kaposi further distinguished lupus vulgaris from lupus erythematosus. When the TB bacillus was identified, and not found in patients with lupus, the association between the two diseases lost favour (Mallavarapu and Grimsley, 2007) .

The neoclassical period began when Kaposi described the systemic nature of SLE. Osler described a disseminated form of the disease which became known as systemic lupus erythematosus (Mallavarapu and Grimsley, 2007). Klemperer's discovery of endocarditis and glomerulonephritis at autopsy led to the term collagen vascular disease (Mallavarapu and Grimsley, 2007).

The discovery of the LE cell by Hargraves in 1948 introduced the modern period (Mallavarapu and Grimsley, 2007). During this time, antinuclear antibody (ANA) and other autoantibodies such as lupus anticoagulant (LA) and the false positive Wasserman reaction (WR) test were discovered (Mallavarapu and Grimsley, 2007).

In 1971, the first classification criteria for SLE was proposed which were then revised in 1982 by the American College of Rheumatology (ACR) (Tan et al., 1982). This revision included the addition of the anti-nuclear antibody test (ANA) and a total of 11 criteria, 4 of which were needed to classify a patient as having SLE, with a minor revision in 1997 to include anti-phospholipid antibodies as part of the immunological criteria (Hochberg, 1997). In 2012, the improved clinically relevant Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) classification for SLE were published (Petri et al., 2012).

The SLICC criteria include a wider spectrum of clinical features of lupus, especially with respect to the skin and neurological features, and serological features including C3/C4 hypocomplementaemia. In addition, patients solely having immune complex glomerulonephritis and a positive ANA and/or anti-dsDNA antibodies, commonly seen in people of African extraction, can be classified as SLE. These criteria have better sensitivity than the ACR criteria (Tikly and Navarra, 2008, Petri et al., 2012)

The clinical course of SLE comprises periods of flares and remissions, with outcomes ranging from remission to death (O'Neill and Cervera, 2010). The clinical presentation of SLE ranges from predominantly cutaneous manifestations to life threatening organ involvement (O'Neill and Cervera, 2010, Tikly and Navarra, 2008). Risk factors for severe major organ involvement include early age of onset and African or Asian ancestry (Wadee et al., 2007, Tikly and Navarra, 2008).

The prevalence of SLE in South Africa is estimated to be 12.2/100 000 population (Morrison et al., 1990). Prevalence rates range from 14.6-78.5/100 000 population in North America to 159/100 000 population in Puerto Rico (O'Neill and Cervera, 2010). Both the incidence of SLE and survival rates of patients with SLE have increased over the decades (Cervera et al., 1999). This improved survival, together with the rising use of potent drugs including corticosteroids (CS) and immunosuppressive agents, has led to increased recognition of comorbidities (Cervera et al., 1999). Early recognition of those patients at risk of comorbid conditions is important to determining a preventative management strategy (Morrison et al., 1990).

Despite the improvement in both the treatment of SLE and survival rates, the outcomes in South Africans is poorer than in industrialised countries (Wadee et al., 2007). The spectrum of comorbidities found in South Africans also differs to those seen in the industrialised, Western world (Tikly and Navarra, 2008). Moreover, SLE may mimic or be mimicked by a range of comorbid conditions, especially HIV in the South African setting (O'Neill and Cervera, 2010).

1.2 Literature Review

Although SLE occurs globally, several studies suggest that the disease is more severe in people of African descent; survival rates are lower and the mean age of onset is earlier (Gabriel and Michaud, 2009, Lau et al., 2006, Wadee et al., 2007, Fernandez et al., 2007). In industrialised, Western white populations, 5-year survival rates are in excess of 95%, with infection and thrombotic events being the most common causes of death (Cervera et al., 1999). In contrast, the 5-year survival rate in Black South Africans has been estimated to be 72%, at best. Mortality in SLE may be due to disease activity, treatment or comorbid conditions (Tikly and Navarra, 2008, Bernatsky et al., 2006)

Mortality in patients with SLE in industrialised countries has a bimodal distribution. Early deaths are mainly caused by infection and disease activity and beyond five years, death is mainly attributed to malignancy and cardiovascular disease (CVD) (Abu-Shakra et al., 1995). In South Africa, this bimodal distribution is not as apparent and the majority of deaths arise from infection, renal involvement and disease activity (Tikly and Navarra, 2008). Mortality from CVD and malignancy seen in industrialised countries does not account for late deaths in South African SLE patients (Wadee et al., 2007). These differences are multifactorial and include genetic factors, disease severity and socioeconomic disparities (Tikly and Navarra, 2008).

Numerous studies in various populations have shown that comorbidities are common in SLE, but the spectrum varies in different populations. In industrialised, Western

populations, CVD is the commonest comorbidity followed by infections (27%), hypertension (11.3%), osteoporosis (OP) (7.5%), Type 2 diabetes mellitus (DM) (2.7%) and malignancies (0.7%). Less common are gastrointestinal bleeds, cataracts, avascular necrosis of joints (AVN) and retinopathy (Cervera et al., 1999). Data from a Puerto Rican study, exhibited similar findings, with some comorbidities occurring more commonly in older age groups. Hypertension (HPT), DM, coronary artery disease (CAD) and OP featured prominently in the older group of patients. In addition, hypothyroidism and end stage renal disease (ESRD) were seen irrespective of age in 19% and 2.1% of the study population respectively (Molina et al., 2007). In the Taiwanese, sepsis is the leading cause for acute morbidity (42.1%) and nephropathy the commonest chronic comorbidity (35.1%) (Kang et al., 2012). In developing countries, including South Africa, infections are a frequent comorbidity. Many patients have lupus nephritis as part of their initial diagnostic criteria (Tikly and Navarra, 2008, Wadee et al., 2007) .

Cardiovascular disease is the leading cause of morbidity and mortality in SLE patients in Western countries, with coronary artery events being up to fifty-fold higher than the general population in the 35 – 44 year age group (Fangtham and Petri, 2013). The risk for CVD was 2.66 times higher in patients with SLE when compared to the Framingham general population (Fangtham and Petri, 2013). Inflammation associated with SLE is an independent risk factor for CVD, and in combination with traditional CV risk factors, predisposes to premature atherosclerosis (Fangtham and Petri, 2013, Duran et al., 2007, Thorburn and Ward, 2003). Cardiovascular morbidity, a common cause for hospitalisation of SLE patients, encompasses a diverse range of diseases such as acute myocardial infarction (MI), congestive cardiac failure (CCF),

cerebrovascular accidents (CVA) and other thrombotic events (Thorburn and Ward, 2003). As many as 3–15% of SLE patients in American studies experienced non-fatal CVAs or strokes, with an overall 20% increase in stroke risk (Thorburn and Ward, 2003, Pyrpasopoulou et al., 2012).

The metabolic syndrome (MetS) has been found to be more common in young patients with SLE, with a prevalence of 18-32%, which is higher in comparison to controls (Thorburn and Ward, 2003). Obesity itself is independently associated with inflammation and impaired functional capacity (Oeser et al., 2005). Predictors of the MetS include CS dose, older age, ethnicity, renal involvement and use of immunosuppression (Thorburn and Ward, 2003).

Osteoporosis, which increases the risk of bone fractures, is common in SLE patients. The reasons are multiple and include CS use, inactivity, chronic inflammation, renal involvement and vitamin D deficiency (Garcia-Carrasco et al., 2009). A South African study has shown that SLE itself causes trabecular bone loss which is independent of CS use (Kalla et al., 1993). Numerous studies have shown reduced bone mineral density (BMD) in SLE patients and the prevalence of OP varying between 3 - 42%. Furthermore, in one study, 42% of SLE patients had a history of at least one symptomatic bone fracture; a 50-70% increase compared to population controls (Oeser et al., 2005).

Comorbid infections are attributed to both the underlying disease and therapy thereof. They occur throughout the course of SLE, often irrespective of disease

activity. The most common sites of infection found in Mexican studies were the genitourinary tract, skin, lung and musculoskeletal systems (Zonana-Nacach et al., 2001). The majority of these infections were bacterial (42%), and most were minor, not requiring hospitalisation. Susceptibility to infection varied depending on disease activity, steroid use, renal involvement and hospitalisation (Zonana-Nacach et al., 2001).

The incidence of tuberculosis (TB) in SLE patients is up to seven fold higher than in the general population, with immunocompromised patients having a higher risk of extra-pulmonary TB (Hodkinson et al., 2009). Risk factors for developing TB include black ethnicity, central nervous system involvement (CNS), lymphopaenia, hypocomplementaemia and CS use (Hodkinson et al., 2009). The majority of patients who developed TB were diagnosed within the first two years of their SLE diagnosis. The spectrum of TB differs in SLE patients, with extensive pulmonary disease, disseminated disease and a high relapse rate more commonly seen than in patients with TB but without SLE.(Hodkinson et al., 2009).

Although HIV is an uncommon comorbid infection, it poses both a therapeutic and diagnostic challenge in those patients who are infected. In one study, patients with coexisting HIV and SLE, 54.7% were diagnosed with HIV prior to the diagnosis of SLE and 75.5% had SLE remission with HIV progression. SLE flares were seen after the initiation of antiretroviral drugs and an increase in viral load was seen following cyclophosphamide as a treatment modality (Carugati et al., 2013). HIV and SLE have several clinical features in common and HIV is a cause of a false positive ANA (Tager and Tikly, 1999).

Malignancies are an important comorbidity, seen more commonly in industrialised countries (Turesson and Matteson, 2013). Both haematological and solid organ tumours are more common in SLE patients compared to the general population, varying between 3.2-11.4% (Sultan et al., 2000, Liang et al., 2012). Risk factors include inflammation, oncogene overexpression, viruses, longer disease duration and certain treatment modalities, such as cytotoxic agents (Turesson and Matteson, 2013). The risk of cancer in SLE patients appears to be higher in those below 40 years of age and the risk decreases with age (Chen et al., 2010). Chronic activation of B and T cells in autoimmune diseases is thought to, in part, cause lymphoproliferative malignancy (Turesson and Matteson, 2013). Abnormal pap smears seen in SLE patients are associated with an increase in the risk of cervical cancer, 3.5 fold compared to the general population (Bernatsky et al., 2012).

Psychological comorbidities such as mood, panic and anxiety disorders are common in female patients with SLE. In one study, 47% of the study sample had a major depressive disorder (Bachen et al., 2009). In cohort studies in the Taiwanese population, elderly male SLE patients have shown a higher risk of developing chronic obstructive pulmonary disease. However, smoking was an important confounder (Shen et al., 2014). Patients with SLE may have an increase in hearing and vestibular disorders with many of these patients suffering from recurrent headaches and migraines (Batuecas-Caletrio et al., 2013).

Treatment options for SLE have advanced over the years. The modalities of treatment may either cause or exacerbate comorbid conditions (Fangtham and Petri, 2013). Corticosteroids (prednisone), even at a low dose have been associated with

infection, cardiovascular events, DM and OP (Hodkinson et al., 2009). All of the immunosuppressive agents predispose to cytopaenias, malignancy and infection, especially herpes zoster (Cervera et al., 1999, Fangtham and Petri, 2013).

Morbidity and mortality may be attributed to either SLE itself or to comorbid conditions. Scoring systems give each condition a weight thereby morphing it into a single score that can be measured against an outcome (Jonsen et al., 2011). Although many comorbidity scores have been tried, the Charlson Comorbidity Index (CCI) has been validated in many studies and is most widely used (Charlson et al., 1987). Developed in 1984, it predicts ten year mortality by calculating a score based on age and range of clinical conditions that increase mortality. The CCI is used to predict prognosis in patients with multiple cumulative comorbid conditions (Charlson et al., 1987) . The CCI has been used in studies looking at renal disease, liver disease and malignancy (Romero-Diaz et al., 2011). However, one of its shortcomings in the context of SLE is that the CCI does not include comorbidities like HPT and infection which are frequently seen in SLE patients. The CCI does however incorporate 17 common comorbidities, giving different weighting to mild and severe disease (Romero-Diaz et al., 2011). A number of disease activity scores are used in clinical practice such as the SLE disease activity index (SLEDAI) and the SLICC/ACR damage index which measures cumulative major organ damage irrespective of whether this is disease or drug related (Petri et al., 2012).

A number of studies using the CCI have been conducted in various countries. In Ireland, the CCI was used on several occasions to identify CVS comorbidities in various rheumatologic diseases (Mohammad et al., 2010). This study concluded that

these comorbidities impact on treatment as well as complications (Mohammad et al., 2010). A Swedish study utilising the CCI, found that in patients with SLE, comorbidity was an independent indicator for decreased survival (Jonsen et al., 2011). The CCI was an independent factor of hospital mortality in an Asian study (Yang et al., 2014). An American study concluded that comorbid conditions can arise from the disease itself or be due to unrelated factors such as age and pathways common to both SLE and the comorbid condition (Wolfe et al., 2010). Certain conditions found in the CCI were highlighted in this study, especially cardiovascular events, gastrointestinal disease and diabetes (Wolfe et al., 2010). An American study, looking at short term predictors of mortality, concluded that the CCI itself is an important predictor and can be used for individual prognosis (Ward et al., 2006). The CCI has also been used as a variable in comparing cohorts of different ages, being worse in the older-onset group (Lalani et al., 2010).

1.3 Aim and objectives

In the context of SLE in SA, there have been a few studies that have focused on causes of hospitalization and death (Wadee et al., 2007), but to date none that have specific focus on comorbidities in SLE.

The aim of this study was to investigate comorbidities in South African patients with SLE.

Primary objective

- The prevalence and spectrum of comorbidities in South Africans with SLE

Secondary objectives

- Using the common comorbidities found in the CCI to identify comorbidities in our study population
- Identifying common comorbidities not included in the CCI
- Predictors of comorbidity

Chapter 2: Patients and Methods

2.1 Study design

Retrospective case record review

2.1.1 Patient Inclusion Criteria

A retrospective case record review of case records of patients attending the Chris Hani Baragwanath Academic Hospital Connective Tissue Diseases Clinic and fulfilling the following inclusion and exclusion criteria

Inclusion criteria

1. Age ≥16 years at diagnosis
2. Fulfilled 1997 ACR classification criteria for SLE
3. Follow up period of at least 6 months
4. Actively attending clinic as at 31 May 2015

Exclusion Criteria

1. No clinical evidence of an overlap connective tissue syndrome
2. Deceased patients

2.1.2 Data abstraction

The following data were abstracted from the case records:

a. Demographics

- Age of disease onset, defined as the age when diagnosis of SLE was confirmed either at the Lupus Clinic, or by a referring specialist physician.
- Gender

- Ethnicity
- Disease duration, calculated as at time from diagnosis to last follow up visit.

b. Clinical and serological evidence of SLE as per 1997 ACR criteria (Appendix A). These criteria were assessed at the time of first diagnosis (baseline) and during the course of follow up (cumulative frequency). Autoantibody status, including anti-dsDNA, anti-Sm, anti -Ro, anti-La, anti-cardiolipin (IgG and IgM) antibodies, lupus anticoagulant and C3/C4 hypocomplementaemia were documented. In the case of patients with lupus nephritis, the renal biopsy results were reported according to the ISN classification.

c. The CCI (Appendix B), and other comorbidities not found in the CCI, including HPT, serious infection, TB, OP and avascular necrosis (AVN) of joints. Hypertension was defined as a blood pressure of greater than 140/90mmHg on at least three occasions or those patients on antihypertensive treatment. Serious infection was defined as infections necessitating hospitalisation and the use of intravenous antibiotic therapy. The diagnosis of TB was based on microbiological evidence or strong clinical and radiological suggestion. Osteoporosis as defined by a bone density scan with a T-score of less than -2.5 or patients with a documented diagnosis of osteoporosis and patients on treatment for osteoporosis. Malignancy as further defined in the CCI. Avascular necrosis as determined by imaging studies (plain radiography or MRI).

d. Drug Therapy

1. Prednisone in varying doses
2. Immunosuppressive drugs including chloroquine, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab and other.

The data was documented as either ever, never or current. High dose prednisone defined as an intravenous steroid pulse or an oral dose of 1mg/kg or more. Low dose defined as an oral dose of less than 7.5mg per day.

2.2 Sample size and statistical analysis

Data was captured using a data capture sheet and was transcribed onto an Excel spreadsheet. When descriptive statistics were parametric, means and standard deviation was used, whereas non-parametric, or skewed data was reported using medians and interquartile range. Categorical data was analysed using the chi-squared test and the Mann Whitney test was used to analyse data that was not normally distributed. The variables were compared to comorbidities at baseline and during the course of disease. A p-value of <0.05 was deemed to be significant. When multivariate log-binomial regression was used, a $p<0.20$ in the univariate regressions were selected (Daniel, 1998, Peduzzi et al., 1996).

2.3 Ethical approval

This study was approved by the Human Research Ethics Committee (Medical), clearance certificate number M140979.

Chapter 3: Results

The majority of patients in this cohort of 200 patients were black female (94%, 94% respectively). The mean age (SD) was 34.6 (11) years with the median duration (IQ range) of disease being 7 years (3.25-12).

The median number of ACR criteria at presentation was 5 whereas during the course of disease, the median criteria fulfilled were 6. The cumulative frequency of ACR criteria and antibody status is shown in Table 3.1. Of the patients who had renal involvement, 46.4% had lupus nephritis class V, 21% class III and 11% class IV.

Table 3.1 Demographic data, clinical features of SLE and autoantibodies

Variable	Cumulative frequency n (%)
Age of onset in years, mean (SD)	34.6 (11)
Duration of disease in years, median	7 (3.25-12)
Gender: female	188 (94)
Ethnicity	
Black	188 (9.4)
Indian	10 (5)
White	2 (1)
ACR criteria	
Malar rash	90 (45)
Discoid rash	91 (45.5)
Oral ulcers	64 (32)
Photosensitivity	82 (41)
Arthritis	148 (74)
Serositis	41 (20.5)
Renal disorder	86 (43)
Neurologic disorder	32 (16)
Haemolytic anaemia	19 (9.5)
Thrombocytopaenia	36 (18)
Leucopaenia	92 (46)
Lymphopaenia	61 (30.5)
Immunologic disorder	160 (80)
Antinuclear antibody (ANA)	199 (99.5)
Autoantibodies	
Anti-dsDNA antibody	76 (38)
Anti-Sm antibody	115 (57.5)
Anti-Ro antibody	105 (52.5)
Anti-La Antibody	53 (26.5)
C3/C4 hypocomplementaemia	108 (54)
IgG anti-cardiolipin Antibody IgG	50 (25)
Anti-cardiolipin Antibody IgM	42 (21)
Lupus Anticoagulant	10 (5)

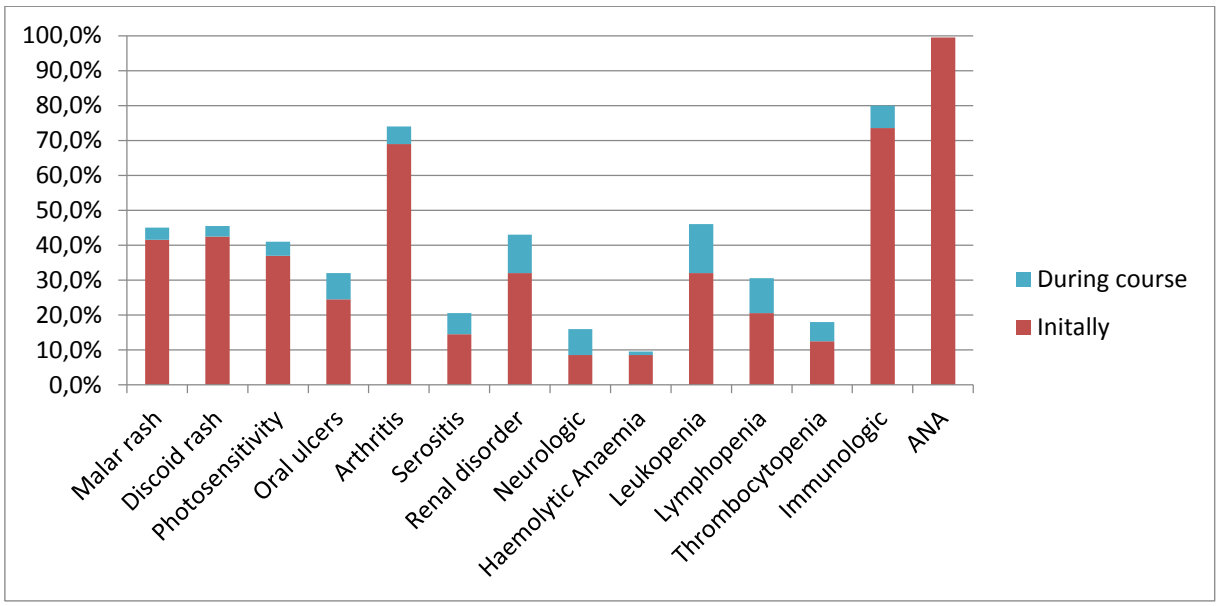

Figure 3.1 Frequency of SLE Features

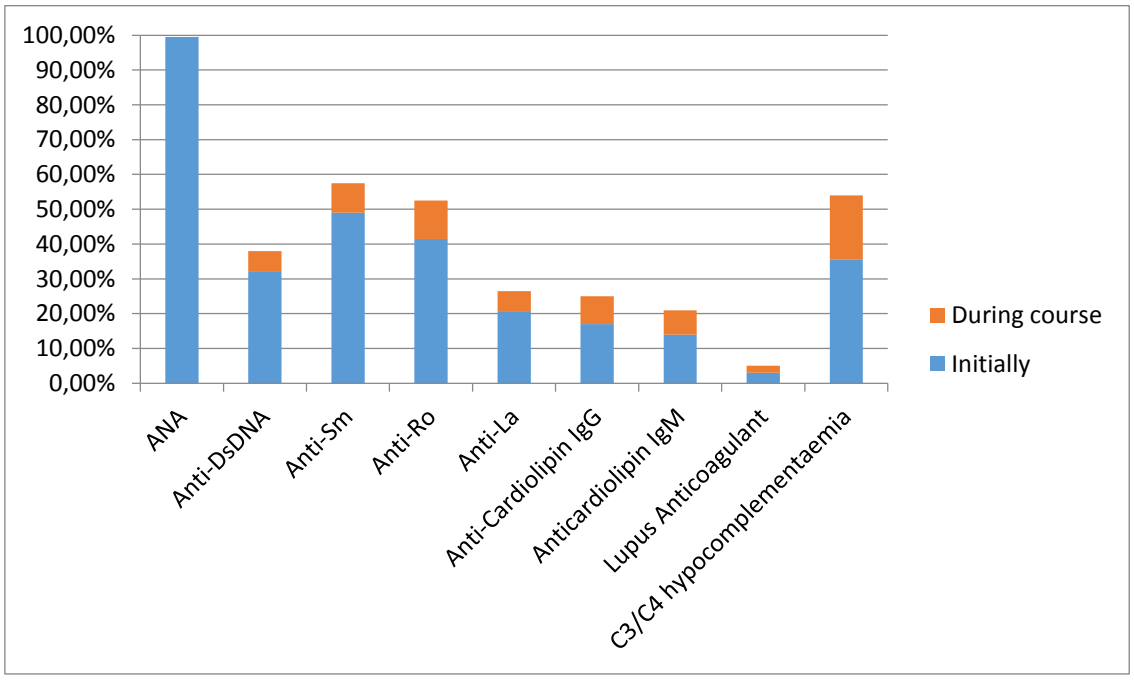

Figure 3.2 Frequency of Autoantibodies and hypocomplementaemia

Immunosuppressive therapy

Table 3.2 Immunosuppressive Agent

Immunosuppressant agent	Cumulative frequency n (%)
Prednisone (all strengths)	173 (86.5)
Chloroquine	195 (97.5)
Azathioprine	64 (32)
Methotrexate	68 (34)
Cyclophosphamide	40 (20)
Mycophenolate mofetil	48 (24)

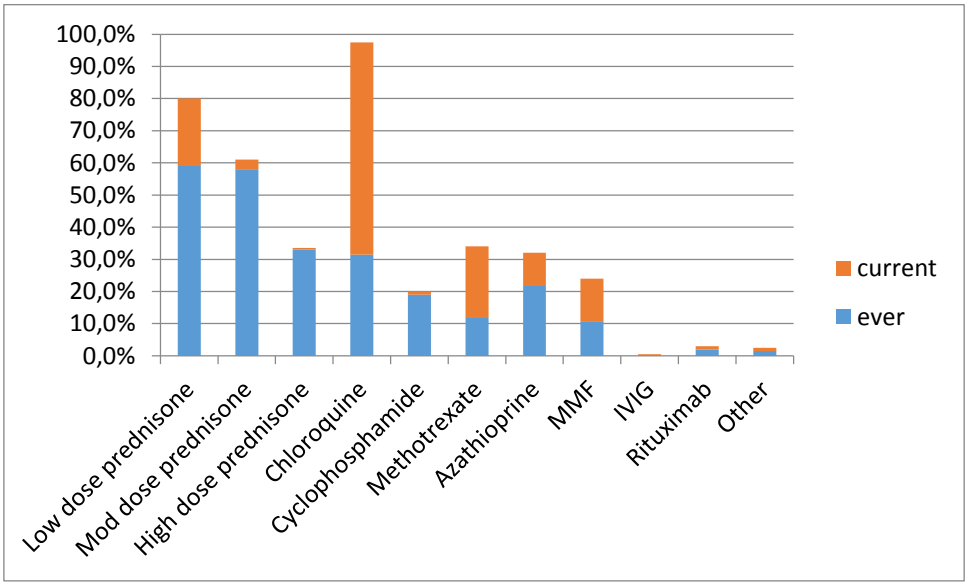

Figure 3.3 Use of Immunosuppressive Agents

Comorbidities

The prevalence of one or more comorbidities at initial presentation was 36.5% (95% CI: 29.8-43.6%) increasing to 56.0% (95% CI: 48.8-63.0%) by the end of the follow up period. The median (IQ range) Charlson comorbidity score was 1 (0-3). One third of patients with TB had extra-pulmonary TB, and of the patients who had serious infection, one third had multiple infections during the course of their disease. The spectrum of comorbidities are shown in Table 3.3. The connective tissue diseases referred to in the data were either secondary antiphospholipid syndrome or secondary Sjogrens syndrome. Overlap conditions were an exclusion criteria.

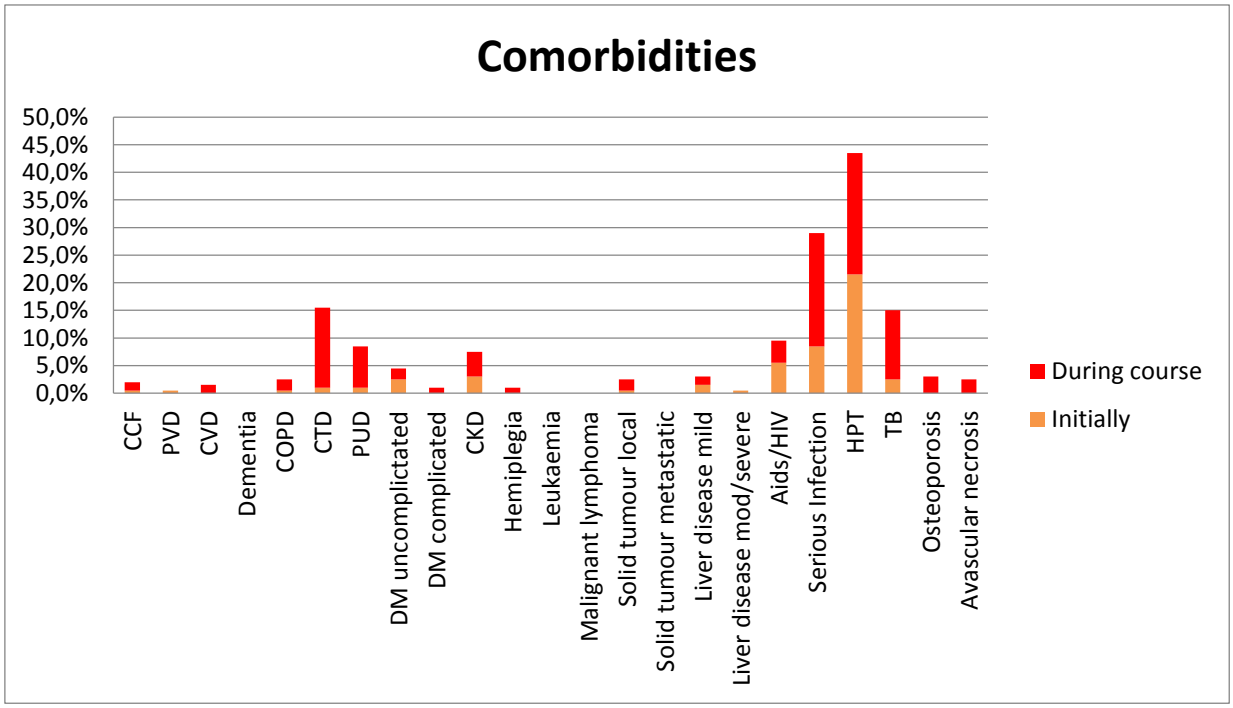

Figure 3.4 Frequency of Comorbidities

Table 3.3 Spectrum of Comorbidities

Comorbidity	Cumulative frequency n (%)
Comorbidities in the CCI	
Myocardial infarction	3 (1.5)
Congestive cardiac failure	4 (2)
Peripheral vascular disease	1(0.5)
Cerebrovascular disease	3 (1.5)
Chronic obstructive pulmonary disease	5 (2.5)
Connective tissue disease	31 (15.5)
Peptic ulcer disease	17 (8.5)
Diabetes mellitus uncomplicated	9 (4.5)
Diabetes mellitus complicated	2 (1)
Chronic kidney disease	15 (7.5)
Hemiplegia	2 (1)
Solid tumour localized	5 (2.5)
Mild liver disease	6 (3)
Moderate/severe liver disease	1 (0.5)
AIDS/HIV	19 (9.5)
Added Comorbidities	
Hypertension	87 (43.5)
Severe infection	58 (29)
Tuberculosis	30 (15)
Osteoporosis	6/14 (42.8)
Avascular necrosis	5 (2.5)

Predictors of comorbidities

Predictors of comorbidity are shown in Tables 3.4 and 3.5.

In patients who initially presented with serious infection, risk factors included the presence of Anti-Ro antibodies and the use of MMF.

For those patients that had HPT at presentation, univariate risk factors included age at onset and renal involvement. Protective factors included fewer number of ACR criteria both initially and cumulatively, as well as the use of low dose prednisone. Multivariate risk factors included age of onset, renal involvement and the use of rituximab. Protective factors were use of low dose prednisone and the number of ACR criteria.

Table 3.4 Comorbidities at initial presentation

Comorbidity	**Risk factor**	**Univariate OR (95 %CI)**	**Multivariate OR (95% CI)**
Severe infection	Presence of Anti-Ro antibodies	3.4 (3.2-9.2)	
	MMF use	3.6 (1.4-9.1)	
Hypertension	Age of onset	1.05 (1.02-1.07)	1.08 (1.04-1.13)
	Renal disorder	2.0 (1.2-3.4)	4.4 (1.8-10.5)
	Initial no ACR criteria	0.86 (0.53-0.86)	0.62 (0.43-0.90)
	Total no ACR criteria	0.62 (0.49-0.80)	0.53 (0.37-0.77)
	Use of low dose prednisone	0.5 (0.29-0.86)	0.46 (0.21-0.99)
	Use of rituximab		17 (1.7-172)

Table 3.5 Cumulative Comorbidities

Comorbidity	Cumulative risk factors	Univariate OR (95 % CI)	Multivariate OR (95 % CI)
Severe infection	No. ACR Criteria	1.25 (1.09-1.44)	
	Anti Sm-antibody	1.75 (1.1-2.7)	1.9 (1.03 – 3.4)
	High dose prednisone use	1.6 (1.1 – 2.5)	
	Cyclophosphamide use	1.6 (1.03-2.6)	2.2 (1.2 – 3.9)
	Methotrexate use	1.7 (1.04-2.8)	
	Thrombocytopaenia	1.9 (1.07-3.3	2.2 (1.2-3.9)
Hypertension	Age of onset	1.03 (1.02-1.04)	1.02 (1.01-1.03)
	Duration of disease	1.03 (1-1.05)	1.05 (1.02-1.09)
	Chloroquine use	1.5 (1.1-2.1)	
	Total no ACR criteria	0.79 (0.65-0.96)	
	Renal disorder	1.4 (1.1-2.0)	1.2 (1.04-1.4)
	CNS involvement	1.6 (1.1-2.3)	
	Presence of anti- cardiolipin IgG	0.43 (0.22-0.84)	0.66 (0.45-0.99)
	Methotrexate use	1.9 (1.2-3.2)	1.8 (1.1-3.0)
	Leukopaenia	1.9 (1.09-3.2)	
Tuberculosis	Use of Azathioprine	2.1 (1.1-4.0)	
	Duration of disease	1.14 (1.07-1.22)	1.16 (1.08-1.25)
	Presence of anti-Ro antibodies	0.43 (0.19-0.94)	
	Hypocomplementaemia	0.27 (0.11-0.63)	0.19 (0.07-0.56)
	Age of onset		0.95 (0.90-0.99)
	Presence of arthritis		0.29 (0.10-0.81)
Connective Tissue Disease	Presence of Anti Ds-DNA	2.8 (1.2-6.8)	
	Presence of Anti-cardiolipin IgG	2.7 (1.2-6.3)	
	Presence of Anti-cardiolipin IgM	2.7 (1.2-6.4)	2.8 (1.3-5.8)
	Presence of Lupus Anticoagulant	3.6 (1.2-10.3)	
	Presence of anti-sm antibodies	0.2 (0.07-0.57)	0.20 (0.07-0.58)
	Use of cyclophosphamide	2.9 (1.3-6.7)	2.8 (1.3-5.9)
Peptic Ulcer Disease	Duration of disease	1.11 (1.05-1.19)	
Chronic Kidney Disease	Use of chloroquine	3.3 (1.2-8.8)	
	Use of cyclophosphamide	3.7 (1.4-9.7)	
	Renal involvement	5.8 (1.9-17.7)	
HIV	Presence of lupus anticoagulant	3.8 (1.1-12.9)	
	Use of chloroquine	2.4 (1.03-5.7)	

Cumulative Comorbidity

Serious infection

Univariate predictors included total number of ACR criteria, the presence of Anti-Sm antibodies, the presence of thrombocytopaenia and leukopaenia and the use of high dose of prednisone, cyclophosphamide, methotrexate and MMF. Multivariate predictors included the use of both MMF and cyclophosphamide, the presence of anti-sm antibodies and the presence of thrombocytopaenia.

Hypertension

Univariate predictors included age at onset, duration of disease, the use of chloroquine, CNS and renal involvement. Protective predictors included the number of criteria and the presence of Anti-Cardiolipin IgG antibodies.

Tuberculosis

Univariate predictors included the use of azathioprine and the duration of disease. Protective predictors included hypocomplementaemia and the presence of anti-Ro antibodies. Multivariate predictors were duration of disease whereas protective predictors were age of onset, hypocomplementaemia and the presence of arthritis.

Connective Tissue Disease

Univariate predictors included the presence of Anti-DsDNA , anti-cardiolipin IgG antibodies, anti-cardiolipin IgM antibodies and lupus anticoagulant as well as the use of cyclophosphamide. The presence of anti-Sm antibodies was protective for CTD.

Multivariate predictors were the use of cyclophosphamide and the presence of anti-cardiolipin IgM antibodies. Once again, anti-Sm antibodies were protective.

Peptic ulcer disease

Duration of disease was a predictor for the development of PUD

Chronic kidney disease

The use of chloroquine and cyclophosphamide were predictive of CKD. Renal involvement was a risk factor for CKD.

Chapter 4: Discussion

In this study cohort of predominantly black females with SLE, just over one third of patients had one or more comorbidities at diagnosis, and this figure rose to almost 60% after a mean follow up of approximately 7 years.

The frequency of clinical features in our study is similar to that seen in other South African studies (Wadee et al., 2007, Dubula and Mody, 2015). As the majority of early deaths in SLE is reported to occur within five years of diagnosis, the median duration of our study was adequate to study comorbidities in this population (Wadee et al., 2007).

South Africa is a country with a heterogeneous population of 54.96 million people (Statistics South Africa, 2015), with elements of both first and third world populations. Chris Hani Baragwanath Hospital has access to all the tests and facilities required to make a diagnosis of SLE, most of which are not available in rural Africa (Tikly and Navarra, 2008). Systemic lupus erythematosus is uncommon in rural tropical Africa and it has been proposed that infections such as malaria may be protective against SLE (Tikly and Navarra, 2008). SLE predominantly affects with theories suggesting a role for both oestrogen and the X chromosome. Genetic susceptibility is shown by monozygotic twins having higher concordance rates and family clustering of cases (O'Neill and Cervera, 2010).

The spectrum of diseases in South Africans with SLE differs significantly to that found in developed countries. The most notable difference between our patient population and that of the developed world is the high burden of serious infection, TB and HPT and the low burden of both malignancy and CVD (Wadee et al., 2007, Dubula and Mody, 2015). Black SLE patients have more severe disease with increased mortality. This may be due to increased comorbidity, socio-economic status, environmental and genetic factors (Bernatsky et al., 2006). Of note, certain comorbidities may be transient. Peptic ulcer disease is a potentially curable condition and steroid related comorbidities may improve with discontinuation of the medication.

Previous studies have focused on mortality in SLE patients but none have looked specifically at the spectrum of comorbidities. Both the disease itself and treatment thereof contribute to mortality in SLE patients (Cervera et al., 1999). Improved survival rates of SLE sufferers, will impact on future development of comorbidities. In this study, mortality was not the focus. European studies have shown that mortality in SLE patients is higher than that in age and sex matched controls. Predictors of mortality were female sex, younger age, a shorter duration of disease and black race (Bernatsky et al., 2006). This fits the demographics of our study population. Previous mortality studies of South African patients with SLE showed that the majority of deaths were attributable to infection (45%) and renal failure (16.4%) with the minority being caused by cardiovascular events (Wadee et al., 2007). In contrast, mortality in European studies revealed an event rate of 3.8, 4.1, 1.5 and 0,6 per 1000 person-years for active disease, cardiovascular events, malignancy and infection respectively (Bernatsky et al., 2006).

South Africa is an endemic TB area with an incidence of 450 000 cases of active TB in 2013 (Kanabus, 2016). As of 2013, TB was the leading cause of death in South Africa (Kanabus, 2016). Up to 80% of South Africans are infected with TB, the majority of who have latent TB infection. The highest prevalence of latent TB is found in young adults living in townships - areas designated during Apartheid for black South Africans (Kanabus, 2016). Patients with SLE are already immunocompromised and therefore at higher risk for TB. A study conducted in Durban, South Africa showed that 12% of hospital admissions in SLE patients with infections, were from TB (Dubula and Mody, 2015). This is comparable to the 15% seen in this study. In keeping with other studies, one third of patients had extra-pulmonary TB, however lymphopaenia was not found to be predictive of TB, unlike prior reports (Hodkinson et al., 2009). Lymphopaenia, with a frequency of 30.5% in our study, is seen in up to 50% of African patients (Tikly and Navarra, 2008). Predictors of TB shown in a previous South African study included black ethnicity, lymphopaenia, C3/C4 hypocomplementaemia, CNS involvement, corticosteroid use and use of immunosuppressive drugs. Multivariate analysis showed that independent risk factors were lymphopaenia, corticosteroid use and duration of corticosteroid treatment (Hodkinson et al., 2009). Despite the high background prevalence of TB, isoniazid prophylaxis was issued to only 2.2% patients in the above mentioned study (Hodkinson et al., 2009). In comparison, this current study analysis showed the use of azathioprine and the duration of disease were predictors of TB. Conversely, an older age of onset, presumably with less drug exposure was protective. Longer duration of SLE and the use of immunosuppressants, was associated with a greater risk of TB. Patients who are older at diagnosis and who have milder disease have lower TB rates, probably related to less exposure to prednisone and other

immunosuppressants. Hypocomplementaemia and the presence of anti-Ro antibodies were also protective.

The cumulative frequency of severe infection was 29% in this study. This is a high burden of infection, especially considering that one third of subjects had multiple infections. A study in a similar population group in Durban, concluded that 35.2% and 17.7% of admissions were for infections and a combination of infection and active disease respectively (Dubula and Mody, 2015). Of these admissions, 14.4% died from severe infections, including TB, pneumonia, urinary tract infections and soft tissue infections (Dubula and Mody, 2015). Predictors of severe infection in the abovementioned study were greater number of ACR criteria met, auto-antibody status, immunosuppressant use and more severe SLE. In comparison, this current study showed that in addition to the number of ACR criteria, auto-antibody status and immunosuppressant use, thrombocytopaenia and leukopaenia are also predictors for serious infection. Infections are the main contributor to morbidity and mortality in developing countries and the susceptibility arises from both the disease itself and the treatment thereof. Often, there is not ready availability of costly supportive health care services such as intensive care units, which impacts on both morbidity and mortality (Bernatsky et al., 2006). Furthermore, our patients are not able to access hospital care in a timeous manner, and this delay in treatment results in more advanced, complicated disease presentations.

South Africa has a high prevalence of HPT. In 2010, the estimated prevalence was over 40% in those older than 25 years (Statistics South Africa, 2015). This is similar to the cumulative frequency of 43.7% in the study population. Those patients with renal involvement were more likely to either have HPT at diagnosis or develop it

during the course of disease. Other predictors of hypertension were older age of onset and CNS involvement. Patients who had fewer ACR criteria without renal involvement, and who required lower doses of prednisone were unlikely to have HPT. Despite the high cumulative frequency of HPT, the cardiovascular comorbidities seen in industrialised countries were not evident in this study which probably reflects the demographics of the young female study population. Previous European studies showed an 11.3% frequency of HPT, well below that seen in the current study. Renal involvement in the same group of patients was only 22.2%; despite the relatively low frequency of HPT and renal involvement, almost a quarter of mortality was from cardiovascular events (Cervera et al., 1999).

The secondary connective tissue diseases seen in this study included Sjogrens syndrome and Anti-Phospholipid Syndrome (APS). Anti-Sm antibodies are specific for SLE and patients with this auto-antibody therefore do not have secondary CTD. Patients with anticardiolipin antibodies often have APS and are often sicker and require the use of powerful immunosuppressants such as cyclophosphamide.

This study found that those patients with CKD were more likely to be on highly potent immunosuppressive drugs, whilst lupus nephritis was causally related to CKD.

Malignancy, especially haematological cancers are one of the more common comorbidities seen in developed countries. In this study, no patients had haematological malignancies, and the only solid tumours seen were Kaposi sarcoma (KS) in one HIV positive patient and local cervical cancer. This may reflect the young age of the patient population and a relatively short follow up time. As both KS and

cancer of the cervix are AIDS defining illnesses, the spectrum of malignancy highlights the burden of HIV in our community. In American studies, a 2-3 fold increase in non Hodgkin's lymphoma is seen with a standardised mortality ratio of 2.8 in comparison with controls (Bernatsky et al., 2012). Theories for the increase in haematological malignancies include translocation of oncogenes, the immune system's ability to promote oncogenesis and chronic inflammation which alters the immune system (Bernatsky et al., 2012).

The Soweto population is changing. What was once a relatively rural community, named in 1963 and formed to accommodate black residents from rural areas, has now transformed into a more urban community. This change has brought with it an increase in non-communicable diseases such as diabetes and CVD. Although this urbanisation has advantages in terms of socio-economic empowerment, it brings with it a "triple threat" of CVD as shown in the Heart of Soweto Study (Sliwa et al., 2008). The morbidity from cardiovascular disease is caused by HIV, infectious diseases and now from the more traditional cardiovascular risk factors. In the future, the bimodal pattern of mortality seen in first world nations may also apply to the South African population. This study however failed to show the cardiovascular morbidity shown in overseas studies.

The CCI is one of the tools used to predict mortality based on a range of comorbidities. Most of our patients had a low CCI score, with the most common comorbidities being those conditions not included in the original score such as HPT and severe infection. The CCI has been extensively validated in many studies for a range of conditions. It has also compared favourably to other indices, however in our population group it was not as useful as anticipated due to the extremely low

prevalence of both cardiovascular events and malignancies. First world studies report a higher prevalence of these diseases and the CCI would better predict mortality in these populations. In a Swedish study, the CCI score was an independent risk factor for mortality in SLE patients and demonstrated a direct relationship between comorbidities and mortality in SLE (Jonsen et al., 2011).

One of the major complications of SLE is organ dysfunction, which impacts on morbidity and mortality (Ruiz-Irastorza et al., 2012). Previous studies looking at causes for hospitalisation showed that infections, renal failure and the disease itself accounted for the majority of admissions (Thorburn and Ward, 2003). Patients with more severe SLE, as evidenced by renal and neurological manifestations, are treated with more potent immunosuppression. This does not come without risks. It was found that cyclophosphamide use increased both the risk of lymphoma and bladder cancer (Bernatsky et al., 2012, Ruiz-Irastorza et al., 2012). This highlights the complexities associated with selecting an appropriate treatment modality, whilst considering the risk-benefit profile.

Corticosteroids are commonly used in the treatment of SLE. This study showed that 86.5% of the cohort used steroids as part of the treatment regime. Although the use of immunosuppressive agents has increased survival, they come with their own complications and may cause organ dysfunction and impact on quality of life (Garcia-Carrasco et al., 2009, Ruiz-Irastorza et al., 2012). Corticosteroid use itself can cause or contribute to a number of serious comorbidities included in this study. Osteoporosis, DM, AVN and HPT can occur as a direct consequence of long term steroid use. Moreover, corticosteroid use can augment the existing increased risk of

infection and malignancy associated with SLE (Bernatsky et al., 2012, Dubula and Mody, 2015). The cumulative dose and duration of steroid treatment impacts on complications; with long term use of high doses associated with greater morbidity (Ruiz-Irastorza et al., 2012). The frequency of OP and AVN was very low in this study. This may be underestimated, as a consequence of a lack of screening for these conditions. In this study population, very few patients had bone densitometry scans, despite being on corticosteroid therapy for prolonged periods of time.

Approximately four million people in South Africa (11.2% of the total population) are HIV positive, with the highest incidence in females of reproductive age (Statistics South Africa, 2015). Systemic lupus erythematosus predominantly affects young females in the same age group, however the frequency of HIV in this population is lower compared to that in the general South African population (Tikly and Navarra, 2008). The cumulative frequency of HIV was 9.5% in our study population – well below the 25% found in the same age group in the general population (Statistics South Africa, 2015). This may reflect the health behavior of SLE patients or the interplay between the two disease entities. Patients with concurrent HIV at SLE diagnosis, or who contracted HIV during the course of their disease seem to have milder disease with fewer complications (Mody et al., 2014). Problems arise when trying to distinguish the symptoms of HIV and SLE as both may have similar manifestations (Tikly and Navarra, 2008, Mody et al., 2014). Apart from the clinical overlap, autoantibodies may be falsely positive in HIV positive patients and false positive HIV results may occur in SLE patients (Mody et al., 2014). The number of ACR criteria fulfilled by HIV positive SLE patients is higher. Whether this is due to SLE itself or the overlapping features of both diseases remains unclear (Mody et al., 2014). The biggest problem arises with treatment of the HIV positive SLE patient. A

low CD4 count from HIV is protective of autoimmune diseases but the potent immunosuppressants used for the treatment of SLE may worsen the symptoms of HIV (Mody et al., 2014). HIV needs to be routinely screened for in the South African SLE population as early diagnosis and treatment with readily available highly active anti-retroviral agents (HAART) can prevent both opportunistic infections and complications of HIV (Mody et al., 2014).

Limitations of the study include a relatively small sample size of 200 patients. As with any retrospective study, information was abstracted from case records, which may not have been complete. As screening for each comorbidity on the CCI is not done routinely, patients may have a comorbidity that is not recorded in the case files. Some patients may have received treatment for conditions other than lupus from other specialist clinics which may not have been recorded. Height and weight was not consistently documented in the files and therefore BMI could not be calculated. Obesity is an important morbidity in developed countries, which not only impairs functional capacity, but also increases inflammation (Oeser et al., 2005). Screening for malignancy was not documented in the files. Since the malignancy found most commonly in this relatively young female study population was localized cervical cancer, perhaps the human papilloma virus vaccine should be offered as part of preventative care. As most patients are on corticosteroid therapy, objective evidence of OP and AVN should be sought.

Chapter 5: Conclusion

In this study of predominantly black females, comorbidities were common but the spectrum differs to those reported in industrialised, Western countries. There is a high burden of comorbidities in South African SLE patients, with the prevalence of one or more comorbidities during the course of the disease being 56.0% (95% CI: 48.8-63.0%).

Most notable is a high prevalence of HPT and severe infections, including acute infections requiring hospitalisation and intravenous antibiotic use, as well as TB. The results suggest that SLE patients with higher disease burden (more ACR criteria and immunologic markers) are more likely to develop severe infections. Furthermore, younger patients, with more severe disease, requiring more potent immunosuppressive drugs, are at increased risk for TB.

Cardiovascular complications, a major comorbidity reported in industrialised, Western countries, were rare in this study, despite a high prevalence of HPT. Malignancies seen in patients in industrialised countries were also not evident in this population. Osteoporosis and AVN were uncommon comorbidities, reflecting the lack of screening for such conditions.

“I'm tired of having to struggle for what seems to come easily to everyone else”, said Mercedes Lackey. This statement about living with chronic illness holds true for those suffering from SLE. Systemic lupus erythematosus, its treatment and comorbidities,

all contribute to an overall poor quality of life for those afflicted. One hope for the future is that identifying predictors of comorbidities might lead to their prevention.

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Chapter 7: Appendices

Appendix A: ACR Criteria for SLE

The 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criteria	**Definition**
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5.Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *OR* b) Pericarditis—documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed *OR* b) Cellular casts—may be red cell, haemoglobin, granular,

	tubular, or mixed
8. Neurologic disorder	a) Seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b) Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Haematologic disorder	a) Haemolytic anaemia—with reticulocytosis *OR* b) Leukopenia—less than 4,000/mm on 2 or more occasions *OR* c) Lymphopenia—less than 1,500/mm on 2 or more occasions *OR* d) Thrombocytopenia—less than 100,000/mm in the absence of offending drugs
10. Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer *OR* b) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* c) Positive finding of antiphospholipid antibodies on: • An abnormal serum level of IgG or IgM anticardiolipin antibodies • A positive test result for lupus anticoagulant using a standard method

	• A false positive test for at least 6 months confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Appendix B: Charlson Comorbidity Index

Scoring: Comorbidity Component (Apply 1 point to each unless otherwise noted)

1. Myocardial Infarction

2. Congestive Heart Failure

3. Peripheral Vascular Disease

4. Cerebrovascular Disease

5. Dementia

6. COPD

7. Connective Tissue Disease

8. Peptic Ulcer Disease

9. Diabetes Mellitus (1 point uncomplicated, 2 points if complicated)

10. Moderate to Severe Chronic Kidney Disease (2 points)

11. Hemiplegia (2 points)

12. Leukemia – acute or chronic (2 points)

13. Malignant Lymphoma (2 points)

14. Solid Tumor (2 points, 6 points if metastatic)

15. Liver Disease (1 point mild, 3 points if moderate to severe)

16. AIDS/HIV (6 points)

Scoring: Age

1. Age <40 years: 0 points

2. Age 41-50 years: 1 points

3. Age 51-60 years: 2 points

4. Age 61-70 years: 3 points

5. Age 71-80 years: 4 points

Interpretation

1. Calculate Charlson Score or Index (i)

2. Add Comorbidity score to age score

3. Total denoted as ‘i’ below

Calculate Charlson Probability (10 year mortality)

1. Calculate Y = e^(i * 0.9)

2. Calculate Z = 0.983^Y

3. where Z is the 10 year survival

Appendix C: Ethics Certificate

R14/49 Dr Lara Sonia Greenstein

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140979

NAME: (Principal Investigator)	Dr Lara Sonia Greenstein
DEPARTMENT:	Internal Medicine Rheumatology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Comorbidities in South Africans with Systematic Lupus Erythematosus
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M Tickly
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/10/2014

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES