COMORBIDITIES IN A COHORT OF PRIVATELY INSURED SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Declaration

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

Signature

Date 18th January 2023 in Johannesburg

Dedication

To God for making this possible…

Acknowledgments

To my husband, Alain, without whom I would not have made it.

To my children, Yohan and Nkembo, for the times they gave up with me, time to allow me to study.

To my parents, Charlotte and Joseph Ngandu for their love and prayers.

To the rest of my family for their prayers, and their support, both physical and spiritual.

To my supervisors, Dr Kavita Makan and Professor Mohammed Tikly for their guidance.

Presentation arising from this work

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Abbreviations

ACR	American College of Rheumatology
AMI	Acute myocardial infarction
ANA	Antinuclear antibodies
Anti-ds-DNA	Anti double stranded DNA
aPL	Antiphospholipid antibodies
CAD	Coronary artery disease
CCI	Charlson Comorbidities Index
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CTD	Connective tissue disease
CVD	Cardiovascular disease
CVE	Cardiovascular events
DM	Diabetes mellitus
ESRD	End stage renal disease
EULAR	European Alliance of Associations for Rheumatology
HDL	High density lipoprotein
HIV	Human immunodeficient virus

HLA	Human major histocompatibility complex
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD 10. Coding	International Classification of Diseases 10th edition
IFN	Interferon
IHD	Ischaemic heart disease
IL	Interleukin
LDL	Low density lipoprotein
LN	Lupus nephritis
MMF	Mycophenolate mofetil
NAPPI	National Pharmaceutic Product Index
NPLE	Neuropsychiatric lupus erythematosus
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odd ratio
SA	South Africa
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TNF	Tumour necrosis factor
US	United States of America
UTI	Urinary tract infection

Abstract

COMORBIDITIES IN A COHORT OF PRIVATELY INSURED SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Comorbidities in systemic lupus erythematosus (SLE) impact negatively health-related quality of life and life expectancy. We undertook a retrospective study of the burden of comorbidities in privately insured South Africans with SLE.

Methods: Data review of patients insured with Discovery Health Medical Scheme (DHMS), ≥16years at diagnosis, ≥6months follow-up and diagnosed with SLE based on ICD 10 codes. Demographics, drug therapy and comorbidities listed in the Charlson Comorbidity Index (CCI) and other comorbidities occurring commonly in SLE patients were documented.

Results: Of 520 patients with SLE ICD 10 codes, only 207 met the other inclusion/exclusion criteria for data analysis. Most were women (90.8%), median (IQR) age and follow-up duration of 39 (30.3-53.0) and 6.1 (3.7-8.1) years, respectively. All patients had at least one comorbidity, the most frequent CCI comorbidities being pulmonary disease (30.9%), congestive heart failure (CHF) (15%) and renal disease (14.5%). Common CCI comorbidities were hypertension (53.1%), mood and anxiety disorders (46.9%), infections (urinary tract infections (UTI) (37.7%) and pneumonia (33.8%)). Independent predictors of 1) CHF were renal disease (OR=855), dyslipidaemia (OR=15.3) and male gender (OR=43.0); 2) hypertension were age at diagnosis (OR=1.03), type 2 diabetes (OR=4.45) and renal disease (OR=4.34); and 3) mood and anxiety disorders were female gender (OR=3.98), cerebrovascular accident (OR=3.18), UTI (OR=2.39) and chloroquine use (OR=1.94).

Conclusion: Comorbidities in this cohort of privately insured South Africans with SLE were common, with all patients having at least one comorbidity. Hypertension, infections and mood and anxiety disorders were the leading comorbidities.

Keywords: systemic lupus erythematosus, comorbidities, Africa

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Chapter 1: Protocol with extended literature review

1.1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of unknown aetiology characterised by circulating antinuclear antibodies (ANA). It is seen in all populations but has a predilection for young women of child-bearing age (Essouma *et al.*, 2020, Rees *et al.*, 2017). The female to male ratio ranges from 2:1 to 15:1 and the highest incidence is found amongst black Americans (Rees *et al.*, 2017).

1.1.1. Aetiopathogenesis

The pathogenesis of SLE is complex and an interplay of genetic, hormonal, and environmental factors contributes to immune dysregulation, chronic inflammation, and tissue damage (La Paglia *et al.*, 2017, Tsokos *et al.*, 2016).

Class II human histocompatibility complex (HLA) loci are an important genetic risk factor for the disease. Common loci found in people of black ethnicity are *HLA-DRB1*15:03-DQA1*01:02-DQB1*06:02*; and in Caucasians, *HLA-DR2* (*DRB1*1501*) and *HLA-DR3* (*DRB1*0301*) (Hanscombe *et al.*, 2018). Several factors are thought to contribute to the female predilection of SLE, namely SLE-linked single nucleotide genetic polymorphism involved in the immune system, epigenetic changes, and sex hormones (Christou *et al.*, 2019). Environmental factors such as smoking, ultraviolet light, viruses, hormones, and drugs often trigger the disease in genetically prone individuals resulting in immune activation, immune dysregulation and chronic inflammation (Rose and Dörner, 2017). An inability of macrophages to clear nucleic material from apoptotic cells plays a role in the initiation and the propagation of the chronic inflammatory processes by increasing the presence of self-antigens (Mok and Lau, 2003). Imbalances between interleukin 10 (IL10) and interleukin 12 (IL12), and the increased production of interleukin 6 (IL6), interleukin 2 (IL2) and type I interferon (IFN) are important drivers of immune dysregulation. This process culminates in the promotion of B cell proliferation and the skewing of T cell function towards B cell proliferation (Tsokos *et al.*, 2016). The result is a reduction in self-tolerance because of self-antigens and circulating autoantibodies produced by activated B cells (Figure 1). This autoimmune environment leads to chronic inflammation and end organ damage that translates into the clinical manifestations

of SLE and contributes to irreversible organ damage and increased risk of certain comorbidities such as atherosclerosis and infections (Kyttaris, 2010).

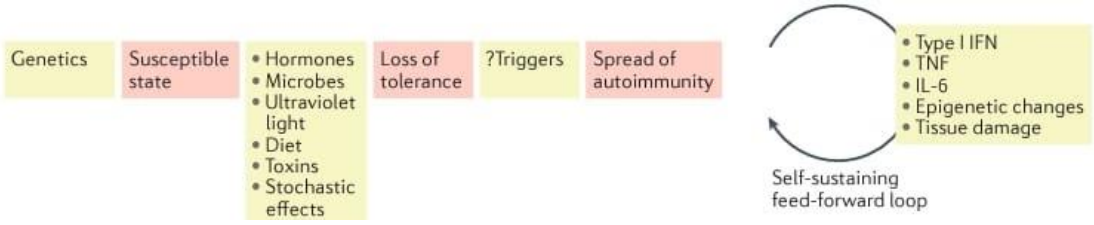

Figure 1. Aetiopathogenesis of systemic lupus erythematosus (Tsokos *et al.*, 2016)

1.1.2. Clinical features and diagnosis

The clinical spectrum of SLE ranges from mild disease with skin and joint involvement to severe disease with renal and neurological involvement. The most common clinical manifestations are skin and joint disease (Fava and Petri, 2019). Severe disease, especially lupus nephritis (LN) and neuropsychiatric lupus (NPSLE), result in major morbidity and mortality (Petri *et al.*, 2012).

The diagnosis of SLE is based on a constellation of clinical features and is supported by the presence of ANA. The latter is now a mandatory criterion in the latest EULAR/ACR classification criteria for SLE (Aringer *et al.*, 2019). Anti-dsDNA and anti-Smith antibodies are associated with LN and antiphospholipid antibodies (aPL) are associated with thrombotic complications and pregnancy loss (Petri, 2020). Other laboratory investigations that contribute to the diagnosis and/or monitoring of SLE disease activity include the serum complement proteins C3 and C4 and direct Coomb's test (Petri *et al.*, 2012).

1.1.3 Treatment and prognosis

Treatment of SLE depends on the severity of the disease. Antimalarials, chloroquine and hydroxychloroquine, are the cornerstone of the management (Fessler *et al.*, 2005). Corticosteroids are used in various doses according to the organ involved; low doses for joint and skin diseases and higher doses for renal disease, serositis, haemolytic anaemia and thrombocytopaenia (Fava and Petri, 2019). Immunosuppressive agents such as

cyclophosphamide, azathioprine and mycophenolate mofetil (MMF) are used as steroid-sparing agents and in more severe conditions such as LN and NPLE (Fava and Petri, 2019, Galanopoulos *et al.*, 2017). More recently biologics such as rituximab, an anti-CD20 monoclonal antibody, and belimumab, an anti-BAFF monoclonal antibody, have been used in cases of refractory thrombocytopaenia, haemolytic anaemia and LN with variable success (Galanopoulos *et al.*, 2017, Kraaij *et al.*, 2018).

In the developing world, infections, hypertension, and heart failure are the commonest comorbidities (Essouma *et al.*, 2020, Tazi Mezalek and Bono, 2014). Infections and LN are common causes of mortality (Essouma *et al.*, 2020, Greenstein *et al.*, 2019, Tazi Mezalek and Bono, 2014). By contrast, a bimodal pattern of mortality was first reported by Urowitz *et al.* in the industrialised countries; where early deaths, occurring in the first five years in SLE patients are primarily due to disease activity and infections and later deaths, beyond five years disease duration, are mainly due to cardiovascular disease (Rees *et al.*, 2016b, Urowitz *et al.*, 1976). With the improvement in life expectancy of SLE patients because of better disease control and judicious use of immunosuppressive therapy, prevention and management of comorbidities has become more important to improve long-term prognosis and health-related quality of life (HRQoL) (Urowitz *et al.*, 2008).

1.2. Comorbidities in systemic lupus erythematosus

Various definitions have been proposed to define comorbidities and most of them have a core theme which refers to comorbidity as " any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study "(Valderas *et al.*, 2009).

Some of the common comorbidities noted in SLE patients in industrialised countries are CVD, osteoporosis, osteonecrosis, malignancies, psychiatric illnesses and infections (Gergianaki *et al.*, 2021, Rees *et al.*, 2016a). Patients with SLE have a higher prevalence of comorbidities compared to the general population (Gergianaki *et al.*, 2021). Comorbidities affect both life expectancy and HRQoL and may appear either before or after the diagnosis of SLE (Arnaud and Tektonidou, 2020, Elera-Fitzcarrald *et al.*, 2018). Certain comorbidities such as thyroid disease, osteoporosis and infections are more common in women whereas pulmonary diseases, CVD, stroke and malignancy are more common in men (Gergianaki *et al.*, 2021, Rees

et al., 2016a). Men are also at greater risk of progression to end stage renal disease (ESRD)(Ramírez Sepúlveda *et al.*, 2019). Men are thought to have a more severe course because of accrued damages (Andrade *et al.*, 2007).

Comorbidities results from a combination of chronic inflammation of SLE and long-term use of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and other immunosuppressive therapy. The latest recommendations by EULAR on the management of SLE dedicate a section on comorbidities highlighting the importance of early diagnosis and prevention of comorbidities (Fanouriakis *et al.*, 2019).

Several instruments including the simple numerical comorbidity count, the Chronic Disease Score/RxRisk, Adjusted Clinical Groups, and the Charlson Comorbidity Index (CCI), have been applied to assess the burden of comorbidities in patients with chronic diseases. The CCI is one of the most widely used instruments (Huntley *et al.*, 2012). The CCI was initially developed to estimate the burden of comorbidities in relation to the 10-year probability of-mortality risks (Charlson *et al.*, 1987). Revisions of the original CCI were published later to adjust for age (Charlson *et al.*, 1994). In 2005 Sundararajan *et al.* further refined the CCI based on the International Classification of diseases 10th edition (ICD 10.) that includes 17 comorbidities in the CCI (Sundararajan *et al.*, 2004). They include: acute myocardial infarction (AMI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), dementia, pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus with or without end organ damage, chronic kidney disease (CKD) , paraplegia, cancer, metastatic cancers, moderate to severe liver disease and human immunodeficiency virus (HIV) (Sundararajan *et al.*, 2004).

In the context of SLE, several studies have used the CCI to assess the burden of comorbidities (Greenstein *et al.*, 2019, Jönsen *et al.*, 2011, Kuo *et al.*, 2019) and it has been validated in various populations including US, Canada, Australia, France, Japan (Charlson *et al.*, 1987, Quan *et al.*, 2011). Quan *et al.* found that the predictive value of the CCI may be affected by rare comorbidities such as HIV in their study population (Quan *et al.*, 2011).

A study in Montreal and showed that the CCI was a predictor of mortality independent of age, activity of disease and damage accrued over the years in SLE (Jönsen *et al.*, 2011). In the UK,

a study comparing the CCI prior to SLE diagnosis and post-diagnosis, found that SLE patients, compared to matched controls for age, gender, clinical practice and duration of follow-up were more likely to have at least one or more comorbidities at diagnosis (38.1% prevalence at diagnosis) and acquired more comorbidities during follow-up (Kuo *et al.*, 2019). The same study highlighted that non CCI comorbidities such as hypertension (21.7%), osteoporosis (12.7%) and depression (18.8%) were the commonest incident comorbidities, more so than CCI comorbidities (Kuo *et al.*, 2019). In a study in Crete, predictors of CCI of one or more were marital status, number of SLE criteria as per ACR 1997 classification criteria and level of education. The most prevalent comorbidities were thyroid disease (45.6%), mental disorders (45.1%) and metabolic diseases (Hypertension (24.6%), dyslipidaemia (33.3%), obesity (35.3%)) (Gergianaki *et al.*, 2021). In a retrospective study of patients seen at a tertiary state hospital in SA, Greenstein *et al.* found hypertension (43.7%), osteoporosis (42.8%) and infections (29%) to be more common than the Charlson comorbidities (Greenstein *et al.*, 2019).

1.2.1. Cardiovascular disease

Cardiovascular diseases that are included in the CCI are AMI, CHF, PVD and cerebrovascular disease. In industrialised countries, CVD are a leading cause of deaths beyond five years disease duration of SLE (Rees *et al.*, 2016b). The spectrum of CVD in SLE ranges from hypertension, CHF, atrial fibrillation, AMI, stroke, angina and claudication (Dzifa *et al.*, 2018, Kariniemi *et al.*, 2021, Magder and Petri, 2012, Yafasova *et al.*, 2021). A large Danish study showed that SLE patients with CHF had a higher mortality compared to their age, gender, and comorbidity-matched controls (Yafasova *et al.*, 2021). In another study, men with SLE were found to be at higher risk of developing CHF (Chang *et al.*, 2020). A US study showed that cardiac causes, especially AMI and stroke represented the second most common indication for hospitalization in SLE patients (Dhital *et al.*, 2020). Although CVD is extremely important as a comorbidity group in general, different population groups have differences in CVD risk. Moreover, in the US, African Americans were found to have an increased risk of CVD compared to Caucasians (Barnado *et al.*, 2018, Grabich *et al.*, 2021). Magder and Petri have shown that even after correcting for traditional risk factors, SLE patients have a higher incidence of CVD, especially in patients younger than 40 years (Magder and Petri, 2012).

Accelerated atherosclerosis in SLE is the result of increased atherogenic damage to the endothelium mediated by oxidative processes, autoantibodies, type 1 IFN, neutrophil extracellular traps and a deficient endothelial repair system (Giannelou and Mavragani, 2017). This together with traditional risk factors such as dyslipidaemia and hypertension, further increase the risk of CVD in SLE (Giannelou and Mavragani, 2017).

1.2.2. Metabolic disease

Diabetes mellitus is common in the general population. Kuo *et al.* found that incident DM (post SLE diagnosis), (4.2%) was more common than prevalent DM (pre SLE diagnosis), (3.1%) (Kuo *et al.*, 2019). This is likely the result of corticosteroid induced DM in patients with a family history of DM, and especially in those treated with high dose corticosteroids (Shaharir *et al.*, 2015).

Dyslipidaemia is common in SLE due to both the disease itself and use of corticosteroids. Dyslipidaemia is linked to disease activity in SLE, and its prevalence can be as high 60% in patients with SLE (Szabó *et al.*, 2017). The pattern of dyslipidaemia in SLE is one of high total cholesterol, high triglycerides, high low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) (Szabó *et al.*, 2017).

1.2.3. Infections

Infections are an important cause of morbidity and mortality in SLE, especially early in the course of the disease (Dhital *et al.*, 2020, Pego-Reigosa *et al.*, 2021). Contributing risk factors include inherent immune dysregulation associated with SLE, use of corticosteroids and immunosuppressive drugs (Feldman *et al.*, 2015). The risk of infections from encapsulated organisms such as *Salmonella* species, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae* is increased in SLE due to functional asplenia (Hepburn and Davies, 2002, Mackenzie *et al.*, 1997). Worldwide SLE patients often present with bacteraemia, respiratory, cutaneous, and urinary infections (Dhital *et al.*, 2020, Pego-Reigosa *et al.*, 2021). Tuberculosis (TB) is especially common in Asia and Africa, related to high prevalence of TB in the general population, and use of corticosteroids (Dubula and Mody, 2015, Hodkinson *et al.*, 2009, Nadda and Singh, 2016, Yang *et al.*, 2017). In SA, some of the risk factors affecting the

general population include smoking, alcohol use, a low body mass index, lower level of education and poor socioeconomic circumstances (Harling *et al.*, 2008).

1.2.4. Malignancies

Patients with SLE have been found to be at increased risk of developing certain malignancies particularly cancer of the cervix and non-Hodgkin lymphoma (Goobie *et al.*, 2015, Wadström *et al.*, 2017). The former is linked to a higher prevalence of human papillomavirus (HPV) infection (Grein *et al.*, 2016). Other factors include inherent immune dysregulation in SLE as well as immunosuppressive therapy in particular cyclophosphamide (Goobie *et al.*, 2015).

1.2.5. Renal disease

Apart from LN being an important cause of renal impairment in SLE, hypertension, diabetes and non-SLE related causes have been shown to be responsible for ESRD in one fifth of patients with SLE (Plantinga *et al.*, 2016). The risk of SLE related ESRD is especially common in men (Ramírez Sepúlveda *et al.*, 2019, Yu *et al.*, 2016).

1.2.6. Bone diseases

Osteonecrosis and osteoporosis are common bone complications found in SLE patients (Edens and Robinson, 2015, Gladman *et al.*, 2018). Both complications result from chronic inflammation, corticosteroid use and a procoagulant state related to aPL (Gladman *et al.*, 2018, Hisada *et al.*, 2019). Compared to healthy individuals, osteoporosis and osteopenia are seen in SLE patients at a younger age (Edens and Robinson, 2015).

1.2.7. Gastrointestinal disease

Peptic ulcer disease is a common complication of chronic NSAIDs used for inflammatory joint disease (Crofford, 2013). The prevalence of PUD in SLE is variable and ranges between 1 to 8% (Greenstein *et al.*, 2019, Kuo *et al.*, 2019). Corticosteroid use was found to increase the likelihood of PUD when used concomitantly with NSAIDs (Luo *et al.*, 2009). Another less common cause of gastrointestinal ulceration in SLE is mesenteric lupus vasculitis, which can present with massive gastrointestinal haemorrhage and requires corticosteroids to control the bleeding (Gayam *et al.*, 2018).

Liver function abnormalities are not uncommon in SLE. Non-specific transaminitis, and very rarely autoimmune hepatitis and primary biliary cirrhosis, can occur in SLE. Important indirect causes of liver dysfunction are medications such as methotrexate, NSAIDs, MMF and azathioprine in the treatment of SLE (Brewer and Kamen, 2018). Acute pancreatitis has been very rarely reported in SLE and is due to either the disease itself or the use of corticosteroids (Gayam *et al.*, 2018).

1.2.8. Pulmonary disease

Chronic pulmonary diseases such as COPD, asthma and interstitial lung disease are not uncommon in SLE (Hansen *et al.*, 2021, Katz *et al.*, 2021, Kuo *et al.*, 2019). A Danish study found that 7.5% of SLE patients had chronic pulmonary disease at the time of diagnosis (Hansen *et al.*, 2021). Taiwanese patients with SLE were more likely to have COPD than the control population (HR 1.73) (Shen *et al.*, 2014). In the US, a longitudinal study showed a prevalence of 19.8% for asthma and 8.3% for COPD (Katz *et al.*, 2021). A recent meta-analysis showed a strong association between asthma and SLE (OR 1.37) (Charoenngam *et al.*, 2021). The likely explanation for this association is the shared hyperreactivity to outside stimuli related to B cell overactivity and the presence of polymorphism of tumour necrosis factor gene (Jiménez-Morales *et al.*, 2009, Sin *et al.*, 2016). Smoking is a known trigger in SLE and a common cause of COPD and therefore might be the link between the two diseases (Katz *et al.*, 2021).

1.2.9. Mental disorders

Mental health problems are increasingly recognised in SLE patients (Gergianaki *et al.*, 2021). Major depression and anxiety disorders are very common in SLE patients (Jorge Asano *et al.*, 2013, Zhang *et al.*, 2017). The prevalence of depression has been estimated to be between 10% and 30% in SLE patients in the UK, Finland and Germany (Albrecht *et al.*, 2021, Hawro *et al.*, 2011, Kuo *et al.*, 2019). The risk of suicide has been shown to be around 10% in SLE especially in patients with poor interpersonal relations and social support (Ishikura *et al.*, 2001, Jarpa *et al.*, 2011). Dementia is uncommon (Kariniemi *et al.*, 2021, Kuo *et al.*, 2019).

Psychiatric disorders in SLE are thought to be multifactorial arising from the disease *per se*, drug therapy (corticosteroids and antimalarials) and lack of social and family support

(Figueiredo-Braga *et al.*, 2018). In recent years, the use of hydroxychloroquine has come under scrutiny because of its link to depression in patients with or without rheumatological disease (Garcia *et al.*, 2020, Mascolo *et al.*, 2018). A study conducted in China showed that close to a third of SLE patients with non-NPLE had depression and this was associated with pyuria, proteinuria and disease activity (Bai *et al.*, 2016).

1.3. African perspective on comorbidities in systemic lupus erythematosus

Only a few studies have focused on comorbidities in SLE in Africans. Alian *et al.* showed that Egyptian patients with SLE had high CCI score with renal disease, PUD and DM as the most common comorbidities and the commonest cause of death was infections (Alian *et al.*, 2019). In a systematic review of native Africans with SLE, Essouma *et al*. found that infections, CHF and hypertension were the commonest comorbidities (Essouma *et al.*, 2020). Several studies have shown tuberculosis (TB) to be a major comorbidity and cause of death in indigent SLE patients living in Sub-Saharan Africa. A retrospective study of 568 SLE patients in Johannesburg, showed that 17% of patients had been diagnosed with TB at least once in the course of their disease (Hodkinson *et al.*, 2009). Similarly, Mody *et al* reported from Durban that 7 out of their cohort of 13 patients with concomitant SLE and HIV had TB (Mody *et al.*, 2014).

In a more recent study, Greenstein *et al.* showed that serious infections and TB are very common and despite a high proportion of patients having hypertension, the impact on ischaemic heart disease (IHD) and stroke was minimal (Greenstein *et al.*, 2019). This in stark contrast to studies in industrialised populations where the burden of CVD in SLE is high (Barbhaiya *et al.*, 2017). Moreover, in South Africa, HIV has been reported with a prevalence of between 2 and 10% of SLE patients (Dubula and Mody, 2015, Greenstein *et al.*, 2019, Ngandu Ntumba *et al.*, 2013). A recent qualitative study by Phuti *et al*. describes the various experiences of South Africans with SLE, a disease that isolates, disfigures with a detrimental effect on mental health (Phuti *et al.*, 2019).

1.4. Comorbidities in large SLE databases

Several studies have investigated the occurrence of comorbidities documented in large lupus databases. A study of 33565 SLE patients on the US Medicaid database showed that infections

were common, occurring in 15% of patients, and that LN, immunosuppressive therapy and male gender were independent risk factors for infections (Feldman *et al.*, 2015). In a further study of the same database, which covers approximately a fifth of the US SLE population, there was an increased prevalence of CVD (Barbhaiya *et al.*, 2017). Strokes were especially common in black patients, whereas AMI occurred mainly in Caucasians.

A study conducted in the UK using the CPRD database assessed the burden of comorbidities in SLE patients and the impact on mortality. They found CVD, neoplasms and chronic renal disease to be prominent. Compared to controls, SLE patients were more likely to have comorbidities at diagnosis, which contributed to an increased risk of death (Kuo *et al.*, 2019).

The major advantage of studying large databases is that a large sample size allows for detection of small and often statistically and possibly clinically significant associations with less obvious comorbidities. However, the major limitation is that diagnosis of clinical conditions is based on disease codes such as ICD 10. and cannot be verified clinically. Moreover, ICD codes for SLE are not necessarily based on SLE classification criteria such as the EULAR/ACR classification criteria for SLE (Appendix A) (Aringer *et al.*, 2019).

1.5. Health system in South Africa

The South African health system is largely a two-tier system, in which about 84% of the population is under the care of the public health sector and remaining 16% of the population serviced by private health sector, mainly through a medical aid schemes (Naidoo, 2012). In the state funded sector, financial and staff constraints often lead to delay in diagnosis and appropriate management (Maphumulo and Bhengu, 2019). Moreover, TB and HIV are a major burden to the health system. By contrast, the overall care in the private sector is similar to that in the industrialised countries (Econex, 2010). In the context of chronic rheumatic diseases, studies in rheumatoid arthritis (RA) in SA have shown major differences in the spectrum of comorbidities between the two sectors. Whilst infections including HIV and TB were found to be common in the public sector, this was not the case in the private sector (Lala *et al.*, 2022). In a study using claims database, a high prevalence of hypertension, dyslipidaemia and hypothyroidism was found (Olivier *et al.*, 2018).

Discovery Health Medical Scheme (DHMS) is the largest open medical aid scheme in South Africa with over 2,8 million beneficiaries in 2019 (DHMS, 2019). Using a similar data mining

approach as the US Medicaid study, the prevalence and possible risk factors of comorbidities of SLE was investigated in DHMS insured South Africans.

1.6. Aim of the study

To determine the burden of comorbidities in a privately insured South African population with SLE.

1.6.1. Primary objective

To identify CCI and other comorbidities in privately insured South Africans with SLE

1.6.2. Secondary objectives

a) Determine predictors of CCI and other comorbidities in SLE patients insured with DHMS
b) Determine gender differences in prevalence of comorbidities and predictors of comorbidities

Chapter 2: Submissible article

COMORBIDITIES IN A COHORT OF PRIVATELY INSURED SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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2.1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterised by multiorgan involvement. With advances in treatment, patients with SLE are living longer, but at the risk of increased comorbidities. These comorbidities are related to both the disease and drug therapies used in the treatment of SLE (Fessler *et al.*, 2005, Urowitz *et al.*, 2008). Comorbidities in SLE not only impact health-related quality of life but also life expectancy (Arnaud and Tektonidou, 2020, Elera-Fitzcarrald *et al.*, 2018). This has led to greater emphasis and awareness of the importance of regular screening and proactive prevention of comorbidities in SLE (Fanouriakis *et al.*, 2019).

The spectrum of comorbidities in SLE vary by disease duration, ethnicity, age and access to health care. Patients with a younger onset of SLE are at greatest risk of developing comorbidities. Cardiovascular disease (CVD), stroke and osteoporosis were more likely in older patients and in those with a longer disease duration (Rees *et al.*, 2016a). Ethno-geographical variation in comorbidities has been observed in several studies. The common comorbidities in SLE patients in the western industrialized world are CVD, malignancies, renal disease and infections (Kuo *et al.*, 2019). In Germany and the UK, depression is common and in Crete, thyroid disease is often seen in patients with SLE (Albrecht *et al.*, 2021, Gergianaki *et al.*, 2021). In the US, African Americans with SLE are more likely to have CVD, strokes, diabetes and renal disease when compared to Caucasian Americans (Barnado *et al.*, 2018, Grabich *et al.*, 2021). In developing countries such as South Africa, hypertension and

tuberculosis (TB) are especially common in SLE patients (Greenstein *et al.*, 2019, Hodkinson *et al.*, 2009).

South Africa has a two-tier health care system in which almost 84% of the mainly indigent population is serviced by the government-funded public health care facilities. The remaining 16% of the population, accesses private health care funded mainly through a private medical insurance scheme (Naidoo, 2012). Previous studies on comorbidities in rheumatoid arthritis (RA) in SA have shown that HIV and TB are common in the public sector whilst less common in the private sector in whom hypothyroidism was common (Lala *et al.*, 2022, Olivier *et al.*, 2018).

A recent study at a tertiary state funded institution showed that hypertension and infections were the commonest comorbidities in SLE patients (Greenstein *et al.*, 2019). In the absence of any published data on comorbidities in privately insured South Africans with SLE, we investigated the spectrum and burden of comorbidities in SLE patients insured with Discovery Health Medical Scheme (DHMS), the largest open medical aid scheme in SA (DHMS, 2019). The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M191128) and by DHMS.

2.2. Patients and Methods

Anonymised data analysed for the purposes of this study were obtained from DHMS (registration number 1125) with the support and assistance of Discovery Health (Pty) Ltd (DH), an accredited administrator and managed care provider for medical schemes.

Patients with ICD 10. codes M32.9 (SLE), M32.19 (SLE with organ or system involvement), M32.14 (glomerular disease in SLE), M32.8 (other forms of SLE), M32.9 (SLE unspecified), M32.12 (pericarditis in SLE) and M32.11 (endocarditis in SLE) were identified excluding those with overlap connective tissue disease (CTD), M32.0 (drug Induced SLE) and L93 (discoid lupus) during the period between January 2008 and December 2017. Only patients ≥16 years at diagnosis and ≥ 6 months follow-up data were included in the analysis.

Comorbidities listed in the CCI and other comorbidities were similarly identified by the appropriate ICD 10 codes (Appendices B and C). All except connective tissue diseases listed in the CCI comorbidities were included in calculating the CCS and CCI. They are acute

myocardial infarction (AMI), congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease, dementia, pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus with or without end organ damage, chronic kidney disease (CKD), paraplegia, cancer, metastatic cancers, moderate to severe liver disease and human immunodeficiency virus (HIV). Age-adjusted CCI scores were calculated using weighted scores for specific comorbidities and an additional point for each decade above the age of 50 years with a maximum value of 4 for patients older than 80 years. This score serves as an estimate of the ten-year survival of patients with multimorbidities (Charlson et al., 1994). In this study patients with mixed connective tissue disease were excluded and therefore no score was added for this comorbidity.

The non-CCI comorbidities documented were infections (pneumonia, meningitis and urinary tract infections (UTI)), TB, hypertension, dyslipidaemia, osteoporosis, osteonecrosis, mood disorders and anxiety disorders. Drug therapies that were documented included chloroquine, oral prednisone, cyclophosphamide, azathioprine, and methotrexate only using the South African National Pharmaceutic Product Index (NAPPI) codes (Appendix D). No biologic agents were captured.

Statistical analysis

Continuous variables were expressed as mean (SD) and median (IQR) for normal and non-normal distributed data, respectively. The Mann Whitney U test was used to compare continuous variables between groups and Chi square/ Fisher's exact two tailed tests for categorical variables.

Univariate and multivariate logistic regression models were used to determine independent predictors of common comorbidities. Adjusted odds ratios, corrected for confounders were calculated. Variables with a P value <0.15 on univariate analysis were included in the multivariate analysis using the enter method of logistic regression analysis. A P value <0.05 was considered to be significant. Statistical analyses were performed using MedCalc for Windows, version 20.009 (MedCalc, Ostend, Belgium).

2.3. Results

Of 520 patients with the relevant ICD 10. codes for SLE in DHMS patient database, 207 met the other inclusion criteria. As shown in Table 1, most patients were women (90.8%), median (IQR) age and follow-up duration of 39 (30-53) and 6.1 (3.7-8.1) years, respectively (Table 1).

Median (IQR) age-adjusted CCI overall was 1 (0-2), indicating an overall ten-year 95% probability of survival. Age adjusted CCI was significantly worse in men compared to women (p=0.04).

Table 1. Demographics and Charlson comorbidity index in 207 South African patients with systemic lupus erythematosus

Variable	All	Women	Men	OR (95% CI)	P value
	n=207	n=188	n=19		
Age, median (IQR) in years	39 (30.3-53.0)	39 (31.0-52.5)	38 (29.3-61.0)	-	0.8
Follow-up, median (IQR) in years	6.1 (3.7-8.1)	6.1 (3.7-8.1)	7.1 (3.7-8.1)	-	0.7
Age-adjusted CCI Ranges					
[0]	51 (24.6)	48 (25.5)	3 (15.8)	1	
[1-2]	86 (41.5)	82 (43.6)	4 (21)	1.28	
[3-4]	47 (22.7)	38 (20.2)	9 (47.4)	0.26	
[≥5]	22 (10.6)	20 (10.6)	2 (10.5)	0.42	0.03
Age-adjusted CCI, median (IQR)	1 (0-2)	1 (0-3)	3 (1-4)	-	0.04
10year probability of survival (%)	96 (77-96)	96 (77-98)	77 (53-96)		

Table 2. Comorbidities in 207 South African patients with systemic lupus erythematosus

Variable	All	Women	Men	OR (95% CI)	P value
	n=207	n=188	n=19		
Cardiovascular diseases					
Acute myocardial infarction	3 (1.4)	2 (1.1)	1 (5.3)	0.2 (0.02-2.2)	0.3
Congestive heart failure	31 (15.0)	23 (12.2)	8 (42.1)	5.2 (2-14) *	0.002
Cerebrovascular accident	27 (13.0)	27 (14.4)	0 (0)	0.05 (0.4-25.7)	0.3
Peripheral vascular disease	0 (0)	0 (0)	0 (0)		-
Hypertension	110 (53.1)	97 (51.6)	13 (68.4)	0.5 (0.2-1.4)	0.2
Neurological and mental disorders					
Dementia	1 (0.5)	1 (0.5)	0 (0)	0.1 (0.01-1.63)	0.2
Paraplegia	2 (1.0)	1 (0.5)	1 (5.3)	0.1 (0.01-1.6)	0.2
Mood and anxiety disorders	97 (46.9)	94 (50.0)	3 (15.7)	5.3 (1.5-19)	0.007
Pulmonary diseases	64 (30.9)	60 (31.9)	4 (21.1)	1.6 (0.5-5.2)	0.4
Gastrointestinal and hepatic diseases					
Peptic ulcer disease	27 (13.0)	27 (14.4)	0 (0)	3.2 (0.4-25)	0.3
Liver disease (all)	4 (1.9)	4 (2.1)	0 (0)	0.4 (0.04-3.9)	0.4
Mild	1 (0.5)	1 (0.5)	0 (0)	0.1 (0.06-1.69)	0.2
Severe	3 (1.4)	3 (1.6)	0 (0)	0.31 (0.03-3.1)	0.3
Metabolic and endocrine diseases					
Diabetes (all)	26 (12.6)	23 (12.2)	3 (15.8)	0.7 (0.2-2.7)	0.7
Complicated	3 (1.4)	2 (1.1)	1 (5.3)	0.19 (0.02-2.2)	0.3
Dyslipidaemia	42 (29.3)	39 (20.7)	3 (15.7)	1.4 (0.4-5)	0.8
Osteoporosis	29 (14.0)	29 (15.4)	0 (0)	3.5 (0.5-26.9)	0.3
Renal disease	30 (14.5)	24 (12.8)	6 (31.6)	3.2 (1.09-9.08) *	0.04
Infections					
HIV	4 (1.9)	3 (1.6)	1 (5.3)	0.29 (0.03-2.9)	0.3
Urinary tract infection	78 (37.7)	72 (38.3)	6 (31.6)	1.3 (0.5-3.7)	0.6
Pneumonia	70 (33.8)	63 (33.5)	7 (36.8)	0.9 (0.3-2.3)	0.8
Meningitis	3 (1.4)	3 (1.6)	0 (0)	0.3 (0.03-3.1)	0.3
Tuberculosis	2 (1.0)	1 (0.5)	1 (5.3)	0.1 (0.01-1.6)	0.2
Neoplasm					
Tumours (all)	12 (5.8)	11 (5.9)	1 (5.3)	1.1 (0.14-9.2)	1
localised	10 (4.8)	9 (4.8)	1 (5.3)	0.9 (0.1-7.6)	1
metastatic	2 (1.0)	2 (1.1)	0 (0)	0.2 (0.02-2.4)	0.3
Avascular necrosis	1 (0.5)	1 (0.5)	0 (0)	0.1 (0.01-1.7)	0.2

*Men versus women

All patients had at least one comorbidity and two third of patients had at least one Charlson comorbidity. The most common Charlson comorbidities were pulmonary disease (30.9%), of which bronchitis (45%) and asthma (36%) were especially common, CHF (15%), and renal disease (14.5%) (Table 2). Hypertension (53.1%), mood and anxiety disorders (46.9%), and infections; UTI (37.7%), and pneumonia (33.8%) were the most common non Charlson comorbidities (Table 2).

With respect to drug therapy, prednisone was prescribed in 80 (68 %) and chloroquine in 131 (63.2%) of patients. Other immunosuppressive drugs included methotrexate, cyclophosphamide and azathioprine in 21%, 1.9% and 11.1% patients, respectively.

Table 3. Independent associations and predictors of major comorbidities in 207 South African patients with systemic lupus erythematosus

Outcome variable	OR (95% CI)	P value
Congestive heart failure		
Male gender	43.0 (2.4-776.2)	0.01
Renal disease	855 (69-10668)	<0.0001
Dyslipidaemia	15.3 (1.4-171.5)	0.02
Type 2 diabetes		
Duration of follow up	1.21 (1.00-1.46)	0.004
Dyslipidaemia	3.57 (1.35-9.48)	0.01
Prednisone	2.47 (1.00-6.07)	0.05
Hypertension		
Age at diagnosis	1.03 (1.00-1.05)	0.02
Type 2 diabetes	4.45 (1.41-14.06)	0.01
Renal disease	4.34 (1.62-11.62)	0.004
Pulmonary disease		
Pneumonia	2.99 (1.56-5.7)	0.001
Dyslipidaemia	2.59 (1.15-5.89)	0.02
Congestive heart failure	0.2 (0.06-0.64)	0.01
Peptic ulcer disease		
Pneumonia	5.49 (2.13-14.18)	0.0004
Type 2 diabetes	4.01 (1.32-12.19)	0.01
Infections		
Urinary tract infections		
Pneumonia	1.95 (1.04- 3.7)	0.04
Mood and anxiety disorders	2.18 (1.19-3.99)	0.012
Pneumonia		
Peptic ulcer disease	2.80 (1.01-7.80)	0.047
Pulmonary disease	2.31 (1.13-4.69)	0.02
Urinary tract infections	2.17 (1.09-4.3)	0.03
Mood and anxiety disorders		
Female gender	3.98 (1.07-14.79)	0.04
Cerebrovascular accident	3.18 (1.2-842)	0.02
Urinary tract infection	2.39 (1.27-4.48)	0.007
Chloroquine use	1.94 (1.03-3.65)	0.04

Independent predictors of the common comorbidities are shown in Table 3. Predictors of CHF were renal disease and male gender. Follow up duration, dyslipidaemia and prednisone use

were independent predictors of type 2 DM. Older age at diagnosis, presence of renal disease and type 2 DM were associated with hypertension. Pneumonia and mood and anxiety disorders were independent predictors of UTI. Predictors of pneumonia were PUD, pulmonary diseases, and UTI. Female gender, chloroquine therapy, UTI and a previous stroke were independent predictors of mood and anxiety disorders.

2.4. Discussion

In this study of privately insured SLE patients, all had at least one comorbidity and 33% of patients did not have any of the conditions included in the Charlson comorbidities. This contrasts with findings in UK and Crete SLE patients in whom 50% or more of patients had no documented Charlson comorbidities (Gergianaki *et al.*, 2021, Rees *et al.*, 2016a). In a South African state funded tertiary hospital, Greenstein *et al.* found that at diagnosis, 36% of patients had at least one comorbidity, and this increased to 56% after median follow up period of 7 years (Greenstein *et al.*, 2019). These differences in the frequency and prevalence of comorbidities are in part attributable to variations in study design and documentation of comorbidities. For example, in the case of the UK study, Read codes, which are a coded thesaurus of clinical terms used by the National Health Service, were used, and in the case of the Greenstein study, comorbidities were extracted from clinical case records (Gergianaki *et al.*, 2021, Greenstein *et al.*, 2019, Rees *et al.*, 2016a).

The median age adjusted CCI in our cohort was 1 (0-2) with a higher score in men compare to women. The higher CCI scores in men compared to women have also been shown by Alian et *al* in an Egyptian study. (Alian *et al.*, 2019). Moreover, that study and a public sector SLE study in SA showed that deaths in SLE patients were associated with higher CCI (Greenstein *et al.*, 2019).

The spectrum of comorbidities in this privately insured cohort differs substantially from that reported in the public sector. The commonest comorbidities in the present study were hypertension, mood and anxiety disorders and chest and urinary tract infections. In some respects, these findings are similar to those in the public sector except that TB and HIV were more common in the latter and pulmonary disease (COPD) had a low prevalence (2.5%) (Greenstein *et al.*, 2019). In other African studies, infections were the commonest comorbidity, but hypertension and CHF had variable prevalence. In a meta-analysis by

Essouma, hypertension and CHF had a prevalence of (10.3-19.6%) and 33.3% respectively and in an Egyptian study the prevalence was 23% and 6.6% respectively (Alian *et al.*, 2019, Essouma *et al.*, 2020).

In line with most Western studies, CVD was common but CAD, a leading cause of death in SLE, was rare despite a high prevalence of traditional CAD risk factors. This is similar to findings in SLE patients in the public sector (Greenstein *et al.*, 2019). However, it is likely that at least some of the patients with CHF had underlying coronary artery disease (CAD) given that the independent risk factors for CHF in the present study were renal disease, dyslipidaemia and male gender. In a US population-based study, Chang *et al.* reported a CHF prevalence of 2.5% in children and adults with SLE. They found that myo-pericardial and valvular disease were risk factors for early CHF, nephritis and hypertension for delayed onset heart failure and black race for both early and delayed onset CHF (Chang *et al.*, 2020).

Pulmonary comorbidities, particularly COPD and asthma have been reported previously to occur in 9.3-19.3% in SLE (Gergianaki *et al.*, 2021, Katz *et al.*, 2021, Kuo *et al.*, 2019). In the present study, of the 30% who had pulmonary disease, a third had asthma. Previous work by Shen *et al.* has shown that patients with SLE were found to have a higher risk of asthma than the general population (Shen *et al.*, 2014) and that asthma negatively impacts on HRQoL (Katz *et al.*, 2021). We were unable to determine the smoking history in our study, but it has been suggested that smoking is the common link between SLE and COPD, as smoking is known to be a trigger for SLE and a risk factor for COPD (Rose and Dörner, 2017, Shen *et al.*, 2014).

Infections are a major challenge globally both in terms of comorbidity and mortality in SLE (Alian *et al.*, 2019, Dhital *et al.*, 2020, Dubula and Mody, 2015). The high risk of infection in SLE patients has been attributed to SLE related immune dysregulation, functional asplenia and drug therapy with corticosteroids and any other immunosuppressive agents (Hepburn and Davies, 2002, Mackenzie *et al.*, 1997). In the present study, about a third of patients had a documented pneumonia and/or urinary tract infection. Dubula *et al.* in a multi-ethnic cohort of hospitalized patients in the public sector in Durban, South Africa showed that infections were common and in contrast to our study, pneumonia was three times more common than UTI (Dubula and Mody, 2015). A recent meta-analysis looking at infection in SLE found that the relative risk of infections in SLE patients is increased by two to six folds compared to the

general population (Pego-Reigosa *et al.*, 2021). Unlike in previous South African studies where approximately one in six patients contracted TB (Hodkinson *et al.*, 2009), TB was rare in the present study. This is likely to be partly related to difference in socioeconomics between the public and private sectors, as TB is more common in lower socio-economic group in the mostly indigent population of South Africa (Harling *et al.*, 2008).

Mood and anxiety disorders have been increasingly recognised in SLE. In some studies up to 40% of patients with SLE have been found to have a mental disorder (Gergianaki *et al.*, 2021) and the prevalence of depression worldwide ranges between 20 and 30% (Kuo *et al.*, 2019, Zhang *et al.*, 2017). A qualitative South African study by Phuti *et al*. looked at various aspects of the life of SLE patients and found that most of them had negative experiences related to SLE and complication thereof, and a fifth of the patients needed referral for management of depression (Phuti *et al.*, 2019). A little less than half the patients in the present study were documented to have a mood and anxiety disorder. These disorders were more common in women, those who had a stroke or UTI and with those treated with chloroquine. A study by Bai *et al.* previously reported an association between urinary symptoms and depression (Bai *et al.*, 2016). In a study by Mascolo *et al.* chloroquine use was associated with neuropsychiatric side effects. Other risk factors for mental health disorders in this study were previous underlying psychiatric disease, female gender, low body weight, alcohol use and concomitant corticosteroid therapy (Mascolo *et al.*, 2018).

Lupus nephritis, often leading to CKD, is especially common in SLE patients of African extraction (Alian *et al.*, 2019, Essouma *et al.*, 2020). Not surprisingly therefore 14.5% of patients in the present study had CKD, substantially higher than the 7.7-9.5% in previous European studies (Gergianaki *et al.*, 2021, Kuo *et al.*, 2019). Moreover, we found CKD to be significantly higher in men compared to women, similar to findings by Ramirez-Sepulveda *et al.* in a multicentre Swedish study (Ramírez Sepúlveda *et al.*, 2019). Although SLE is rare in men compared to women, several studies have shown that SLE in men is more severe (Andrade *et al.*, 2007).

Given that antimalarials form the cornerstone of treatment in SLE (Fessler *et al.*, 2005) and are readily available and affordable, the proportion of patients (68%) documented to have been treated with CQ in the present study was surprisingly low. By comparison, 94.2% of SLE

patients in the South African state sector had been treated with CQ at some point(Greenstein *et al.*, 2019).

An obvious limitation of the study is the diagnosis of SLE and comorbidities which were based solely on ICD 10 codes without case record verification as to whether the patients met any established classification criteria for SLE, such as the SLICC or 2019 EULAR/ACR criteria. Specifically, none of the patients had an ICD 10 code for LN even though 14.5% of patients had CKD. It is conceivable that LN was the underlying cause of renal disease in at least a proportion of patients. Secondly, we were also unable to determine the duration of disease, ethnicity, and smoking, all of which are known to impact on burden and spectrum of comorbidities, especially CVD. Thirdly, in terms of statistical analysis, the relatively small sample size of 207 patients limits the statistical power of the study, for example some of the odd ratio's CI in CHF were wide making it less precise in terms of strength of association. Fourthly, it was not possible to explore the temporal relationship of certain comorbidities, e.g., UTI with mood disorders, to determine a possible causal relationship of one with the other. Finally, we could not access mortality data to determine the relationship between comorbidities on mortality.

In summary, our findings show that comorbidities are common in privately insured South Africans with SLE. However, the spectrum differs from that in the public sector, especially with respect to COPD being more common and substantially less TB and HIV infections. The high occurrence of mental disorders highlights the need for active screening for these disorders in routine clinical practice.

Chapter 3: Conclusion

Systemic lupus erythematosus is a rare disorder affecting especially women. Health-related quality of life and mortality are related to both disease complications such as LN and comorbidities like infections (Elera-Fitzcarrald *et al.*, 2018, Kuo *et al.*, 2019). With advances in treatment of SLE, comorbidities are becoming an increasing challenge especially with regard to CVD (Rees *et al.*, 2016a).

The present study of privately insured South Africans provides further evidence of the burden of comorbidities in SLE where all the patients had at least one comorbidity. The commonest comorbidities were hypertension, infections and mood and anxiety disorders. Of the Charlson comorbidities, pulmonary diseases (asthma, COPD, bronchitis), CHF and renal disease were the most frequent, the latter two had a predilection for men. These findings are to some extent at odds with observations in public sector South African SLE patients where hypertension and infections were the commonest comorbidities and TB and HIV were much more prevalent compared to the private sector (Greenstein *et al.*, 2019).

Unlike in several western populations, CAD appears to be rare despite the high prevalence of traditional risk factors in South Africans with SLE in both the private and public sectors. Whilst this might reflect a true difference with other countries, it is likely that subclinical CVD is underdiagnosed because of cost constraints. By contrast, mental health disorders were common, especially in association with other comorbidities like infections and CVA and use of antimalarial therapy.

Notwithstanding the limitations of the present study, the findings provide further evidence of the burden of comorbidities in SLE in South Africans. They highlight the need for active screening of common comorbidities, especially mental health disorders. Prospective studies are needed to investigate the impact of appropriate screening and interventions of common comorbidities on HRQoL and mortality in South African SLE patients.

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Appendices

Appendix A. Eular/ACR criteria of SLE 2019 (Aringer *et al.*, 2019)

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Appendix B. Charlson comorbidity index and respective ICD codes (Sundararajan *et al.*, 2004)

Condition	Weights	ICD-9-CM	ICD-10-AM
Acute myocardial infarction	1	410, 412	I21, I22, I252
Congestive heart failure	1	428	I50
Peripheral vascular disease	1	441, 4439, 7854, V434	I71, I790, I739, R02, Z958, Z959
Cerebral vascular accident	1	430–438	I60, I61, I62, I63, I65, I66,G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Dementia	1	290	F00, F01, F02, F051
Pulmonary disease	1	490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65
Connective tissue disorder	1	7100, 7101, 7104, 7140, 7141, 7142, 71481(now 5171), 725	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353
Peptic ulcer	1	531, 532, 533, 534	K25, K26, K27, K28
Liver disease	1	5712, 5714, 5715, 5716	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745
Diabetes	1	25002501, 2502, 2503, 2507	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complications	2	2504, 2505, 2506	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Paraplegia	2	342, 3441	G81 G041, G820, G821, G822
Renal disease	2	582, 5830, 5831, 5832, 5833, 5835, 5836, 5837, 5834, 585586588	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25
Cancer	2	14, 15, 16, 18, 170, 171, 172, 174, 175, 176, 179, 190, 191, 192, 193, 194, 1950, 1951, 1952, 1953, 1954, 1955, 1958, 200, 201, 202, 203, 204, 205, 206, 207, 208	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96
Metastatic cancer	3	196, 197, 198, 1990, 1991	C77, C78, C79, C80
Severe liver disease	3	5722, 5723, 5724, 5728	K729, K766, K767, K721
HIV	6	042, 043, 044	B20, B21, B22, B23, B24

The ten-year survival equals 0.983(e(C*0.9)). C is the total CCI of the patient (Charlson *et al.*, 1994).

Appendix C. Non Charlson comorbidities and respective ICD codes

Severe Infections defined as any infections requiring admission and or intravenous antibiotics.

Condition	ICD Codes 10
Antiphospholipid antibodies	D68.61
Chronic kidney disease	N18.1, N18.2, N18.3, N18.4, N18.5, N18.9
Cutaneous infections	L08.8
Hypertension:	I10
Meningitis	G03.9
Mood and anxiety disorders	F30 to 39 and F40-48
Osteonecrosis	M87.9 and M87.1
Osteoporosis	M80 and M81
Pneumonia	J09-18
Urinary tract infections	N39, N30, N30.00, N30.01, N34
Tuberculosis:	A15.0, A15.1, A15.2, A15.4, A15.7, A17.8, A18.0, A18.1, A18.3, A18.4, A18.5, A18.6, A18.7, M49.0

Appendix D. Therapy and respective national pharmaceutic product index (NAPPI) codes

Therapy	NAPPI codes
Azathioprine	701252, 706108, 712609, 700777
Chloroquine	747297, 794333
Cyclophosphamide	723274
Prednisone	788783, 752304,818267
Methotrexate	712504, 742465
Dialysis- dependence on renal dialysis	z99.2.

Appendix E. Specific conditions

Pulmonary diseases (n=64 of 207)	*(%)*
Asthma (Exclude overlap)	35.9
Bronchiectasis	7.8
Bronchitis*	45.3
Chronic obstructive pulmonary disease (Exclude overlap)	4.7
Overlap	6.3
Renal diseases (n=30 of 207)	*(%)*
CKD2	3.3
CKD3	6.6
CKD5	26.6
Chronic kidney disease unspecified	50.0
Other neuromuscular dysfunction of Bladder	3.3
Chronic nephritic sx with diffuse mesangial proliferative GN	3.3
Mood and anxiety disorders (n=97 of 207)	*(%)*
1 disorder *(n=49 of 97)*	50.5
Anxiety disorder	16.3
MDD	77.5
Others	6.1
Multiple mental disorders *(n=48 of 97)*	49.5

Appendix F. Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mbombo Henriette Ngandu Ntumba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191128

NAME: (Principal Investigator)	Dr Mbombo Henriette Ngandu Ntumba
DEPARTMENT:	Internal Medicine Discovery Database
PROJECT TITLE:	Comorbidities in a cohort of privately insured South Africans with Systemic lupus erythematosus
DATE CONSIDERED:	29/11/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Kavita Makan and Prof Mohammed Tikly
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/02/2020

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 Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 22/2/2020

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G. Turnitin

Turnitin Originality Report

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