COMORBIDITIES IN BLACK SOUTH AFRICANS WITH RHEUMATOID ARTHRITIS

Vikash Goolab Lala

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

i. DECLARATION

I, Vikash Goolab Lala, 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. In addition, I declare that it has not been submitted for any other degree or examination at this or any other University.

.....

The ..... day of ....., 2018

ii. DEDICATION

To my parents, Indira and Goolab, for their caring support throughout this project.

iii. PRESENTATIONS ARISING FROM THIS RESEARCH

Oral presentations:

1. 24th Congress of the South African Rheumatism and Arthritis Association - 2015
    - Title: Comorbidities in Black South Africans with Rheumatoid Arthritis
2. University of the Witwatersrand, School Of Clinical Medicine research day – 2015
    - Title: Comorbidities in Black South Africans with Rheumatoid Arthritis

iv. ETHICS CLEARANCE

Permission to undertake this retrospective research study was obtained from:

- Prof. M. Tikly (Head of Division Rheumatology, Chris Hani Baragwanath Academic Hospital)
- Prof. KRL. Huddle (Head of Department, Internal Medicine, Chris Hani Baragwanath Academic Hospital)
- University of the Witwatersrand, Human Research Ethics Committee (Medical). Clearance number: M140882

v. ABSTRACT

Introduction: Comorbidities occur commonly in rheumatoid arthritis(RA) but little is known about their prevalence and spectrum in South Africans.
Objectives: To determine the prevalence and associated risk factors of comorbidities in black South Africans with RA.
Methods: A retrospective record review of black RA patients at a tertiary rheumatology service. The cumulative comorbidity score was assessed using the Charlson comorbidity score.
Results: Of the 500 patients studied, the mean(SD) age and disease duration was 60.0(11.1) and 10.7(5.0) years, respectively. Most patients (50.5%) had severe disability (functional class 3-4) at diagnosis with 98% of patients having had ≥1 comorbidities. The median number of comorbidities was 3.0(IQR 2.0-4.0). Comorbidities were a function of age, follow up duration and disability (p=<0.001). The table below shows the common comorbidities.

	Prevalence (%)		Prevalence (%)
Anaemia	391(78.2)	Tuberculosis	53(10.6)
Hypertension	350(70.0)	HIV (n=204)	44(9.3)
Peptic ulcer disease (PUD)(n=114)	73(64.0)	Congestive heart failure	33(6.6)
Hypercholesterolemia (n=466)	221(47.4)	Cerebrovascular disease	14(2.8)
Osteoporosis (n=132)	62(47.0)	Malignancy	9(1.8)
Diabetes mellitus	77(15.4)	Ischaemic heart disease	3(0.6)
Serious infections	56(11.2)		

Serious infections occurred more commonly in those with osteoporosis (OR-4.32), vasculitis (OR-4.0), anaemia (OR-3.62) and HIV (OR-2.32). Patients with the following comorbidities were more likely to have deceased during follow up: CCF (OR-5.44), serious infections (OR-4.58), interstitial lung disease (OR-3.91), arthroplasty (OR-2.46), TB (OR-2.22) and PUD (OR-1.54).

Conclusion: Despite the high prevalence of cardiac risk factors in this population, the prevalence of ischaemic heart disease remains low. Osteoporosis is commonly found in RA patients undergoing DEXA scans.

vi. ACKNOWLEDGEMENTS

I would like to acknowledge the following people for their continued support and valued guidance in the completion of this research report:

- Dr. N. Govind – for her patience and guidance as a supervisor and for reviewing the research report
- Prof. M. Tikly – for his invaluable inputs, encouragement and knowledgeable assistance with statistics
- Ms. L. Dube – for her kind assistance with data capturing

vii. TABLE OF CONTENTS

viii. LIST OF FIGURES

Chapter 3

Chapter 4

ix. LIST OF TABLES

Chapter 1

Chapter 3

x. NOMENCLATURE

ACPA - Anti-citrullinated peptide antibodies

ACR - American College of Rheumatology

AIDS - Acquired immune deficiency syndrome

BMD - Bone mineral density

CAD - Coronary artery disease

CCF - Congestive cardiac failure

CCI - Charlson comorbidity index

CCS - Charlson comorbidity score

CHBAH - Chris Hani Baragwanath Academic Hospital

CKD - Chronic kidney disease

COPD - Chronic obstructive pulmonary disease

CRP - C-reactive protein

CV - Cardiovascular

CVD - Cardiovascular disease

DEXA - Dual-energy X-ray absorptiometry

DM - Diabetes Mellitus

DMARDS - Disease modifying anti-rheumatic drugs

EULAR - European League Against Rheumatism

FEV1 - Forced expiratory volume in 1 second

FC - Functional class

FVC - Forced vital capacity

GFR - Glomerular filtration rate

HIV - Human immunodeficiency virus

HLA-C - Human leukocyte antigen C

IHD - Ischaemic heart disease

IL - Interleukin

ILD - Interstitial lung disease

IQR - Interquartile range

MI - Myocardial infarction

NSAIDs - Nonsteroidal anti-inflammatory drugs

OP - Osteoporosis

PUD - Peptic ulcer disease

RA - Rheumatoid arthritis

REDCap - Research Electronic Data Capture

RF - Rheumatoid factor

SD - Standard deviation

TB - Tuberculosis

TNF - Tumor necrosis factor

TNFi - Tumor necrosis factor inhibitors

UK - United Kingdom

USA - United States of America

1. CHAPTER 1: BACKGROUND

1.1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of synovial joints with a number of extra-articular manifestations. This results in a broad range of clinical manifestations, often making the management of patients challenging. Comorbidities are common amongst RA patients and pose their own challenges with respect to screening, disability, therapy, treatment choices, morbidity and mortality. An understanding of the spectrum of comorbid diseases and their associated risk factors, aids in managing the patient with RA holistically. Comorbid diseases are well described in industrialized populations. However local South African data are lacking. Due to a variety of reasons, including some differences in the clinical phenotype of RA in black South Africans coupled with specific socioeconomic, environmental and resource limitations, the spectrum and prevalence of comorbidities are likely to be different from industrialized countries.

1.2 Rheumatoid arthritis

1.2.1 Overview

Rheumatoid arthritis is a chronic systemic inflammatory disease which primarily affects the synovial joints. It presents mostly as a symmetrical inflammatory polyarthritis affecting small joints of the hand. Poor or inadequate control of joint inflammation, often leads to joint destruction resulting in joint deformities with subsequent functional impairment (1). Rheumatoid arthritis has an insidious disease onset with early disease typically involving the small joints of the hands and feet. Due to the inflammatory nature of the disease patients commonly report early morning stiffness of the joints which lasts longer than an hour and improves with

physical activity. Despite the synovium being the central target of the disease, RA by virtue of its systemic nature, can be associated with a multitude of extra-articular manifestations.

1.2.2 Epidemiology

The prevalence of RA varies amongst nations with a worldwide prevalence in developed countries of 0.5 – 1%. These figures are influenced by geographical location, ethnicity and gender. Females are affected by the disease two to three times more commonly than men. Data from the United States of America (USA) have shown that although the disease is more prevalent with increasing age, the overall disease prevalence is decreasing in recent years (2).

Earlier studies in black Africans suggested that RA was uncommon and had a mild course (3). More recent studies from predominantly urban populations, show a greater resemblance to Western populations with an increase in severity and prevalence of disease (4, 5). A systematic review of RA patients in Africa had estimated a much lower disease prevalence (0.36%) as compared to the approximated 1% in industrialized caucasian populations (6). Prevalence figures may be inherently lower in African populations due to younger populations, shorter life expectancy and under reporting of the disease. In addition, most South African data were collected during the apartheid era and was thus influenced by political divides and the effects of migrant labour.

1.2.3 Aetiopathogenesis

Although the precise aetiology of RA remains unknown, it is thought to be likely from a combination of genetic susceptibility and environmental triggers. This results in the activation of immune modulators and signaling pathways responsible for the clinical manifestations of the disease.

1.2.3.1 Genetic factors

The association between RA and the human leukocyte antigen DRB1 (HLA-DRB1) has been well established. The majority of patients carry the HLA-DRB1*04 allele with individuals expressing two alleles being at a greater risk for extra-articular disease and nodulosis (7). A number of alleles conferring an increased risk have been identified in rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) positive patients. In contrast, genetic factors in seronegative disease are less well established but still play an important role.

1.2.3.2 Environmental factors

The environmental influence in the pathogenesis of the disease is supported by concordance rates of only 15-30% in monozygotic twins (8). Amongst patients with the HLA-DRB1 allele, smoking increases the risk of developing the disease. Moreover, this combination increases the risk of ACPA positive disease which confers a less favorable prognosis (9). Furthermore, recent work has demonstrated the importance of various gut microbiomes in the development and the progression of RA. Dysbiosis of gut microbiomes have been shown to correlate with auto-antibodies and this microbiome imbalance is partly corrected with the use of disease modifying anti-rheumatic drugs (DMARDS)(10). Other environmental associations such as alcohol, oral contraceptives, vitamin D and red meat consumption lack supporting evidence (11).

1.2.3.3 Immune modulators

The synovium is the epicenter of disease in RA. Synovitis occurs as a result of leukocytic infiltration of the synovium. This is mediated by a variety of immune responses, cytokines and angiogenesis. The innate and adaptive immune systems both play key roles in this response with both cellular and humoral immunity being

implicated. The role of T cells is largely mediated by Th1 and Th17 T cells. Humoral immunity contributes to the pathogenesis of the disease by auto-antibody production, auto-antigen presentation and cytokine production (12).

Several cytokines have been implicated in the disease with interleukin (IL) 1, IL-6, IL-17, tumor necrosis factor (TNF) and vascular endothelial growth factor playing dominant roles. These cytokines are mediators of inflammation and cell migration. Activation of the innate immune system involves a number of effector cells including macrophages, neutrophils, mast cells and natural killer cells. Macrophages have a central role in the development of synovitis (12).

In addition to synovitis, cartilage and bone destruction occurs via several mediators including matrix metalloproteinases and osteoclast activation. Moreover, pannus formation further leads to bone erosions. Angiogenesis, involving vascular endothelial growth factor, is important in pannus development and maintenance (12).

1.2.4 Clinical features

Rheumatoid arthritis usually has an insidious disease onset but can occasionally present in an acute or sub-acute manner. Any joint can be affected but the disease has a predilection for the metacarpophalangeal, metatarsophalangeal, proximal interphalangeal, wrist and knee joints. Disease is typically symmetrical and manifests as early morning stiffness, swelling, pain, tenderness, limitation of movement and deformities. This classically occurs in the hands and to a lesser extent in the feet. Typical deformities include boutonniere deformities, swan-neck deformities, ulnar deviation of the fingers, radial deviation of the wrists, Z deformities of the thumb, piano key deformities of the ulnar styloid, hallux valgus, hammer toes and flattening of the feet. Other musculoskeletal abnormalities include tenosynovitis and

entrapment neuropathies such as carpal tunnel syndrome. The disease may be associated with constitutional symptoms.

1.2.5 Radiological features

Radiologically, early disease may be limited to soft tissue swelling with the subsequent development of peri-articular osteopenia. As the disease progresses joint spaces narrow and juxta-articular erosions develop. Large cystic erosions may manifest in severe advanced disease (13).

Additional imaging modalities such as MRI, grey scale and power Doppler ultrasonography are being increasingly utilized to detect early disease (13). Although clinically useful, these modalities are limited by their availability and cost. Both MRI and ultrasonography are useful in (even prior to their radiographic appearance on X-rays) detecting early synovitis and joint damage. Furthermore, MRI is useful in demonstrating bone marrow oedema and synovial hypertrophy (13).

Ultrasonography is a sensitive tool and thus useful for its negative predictive value (14). The addition of power Doppler ultrasonography has been proven to be a valuable marker of inflammation and disease activity (15).

1.2.6 Extra-articular manifestations

Risk factors for the development of extra-articular disease include smoking, rheumatoid factor positivity and an early onset of physical disability (16). The extent of involvement of extra-articular disease is illustrated in Table 1.1. The risk of developing a vasculitis in RA patients is increased with longstanding disease treated with glucocorticoids (as opposed to with DMARDs), strongly positive rheumatoid factor and smoking (17). Extra-articular disease in RA is a poor prognostic indicator and increases morbidity and mortality (18).

Table 1.1 - Extra-articular manifestations

Cardiovascular disease: - Valvular heart disease - Myocarditis - Cardiomyopathies - Rheumatoid nodules	Neurological disease: - Myelopathies - Sensorimotor neuropathies - Entrapment neuropathies
Ocular disease: - Sicca syndrome - Episcleritis - Scleritis	Dermatological manifestations: - Rheumatoid nodules - Skin ulcers - Neutrophillic dermatoses
Vascular disease: - Vasculitis (digital infarcts, gangrene, cutaneous ulcers, livedo reticularis, purpura and visceral arteritis)	Respiratory disease: - Pleuritis - Pleural effusions - Obstructive lung disease - Interstitial lung disease - Bronchiectasis - Pulmonary nodules
Haematological abnormalities: - Anaemia - Felty's syndrome (neutropaenia, splenomegaly and nodular RA)	Secondary Sjogren's syndrome
	Renal involvement

1.2.7 Diagnosis

There are no diagnostic criteria for RA. Instead classification criteria, which have been developed primarily for research purposes, are often used to make a clinical diagnosis of RA. The classification criteria have evolved over time with the earliest being the 1958 Rome criteria, followed by the American College of Rheumatology (ACR) 1987 criteria and most recently the 2010 ACR/EULAR (European League Against Rheumatism) classification criteria (19). The 2010 criteria have a better

sensitivity for early disease whereas the 1987 ACR criteria (20) have a better specificity for established disease.

Table 1.2 - 1987 ACR criteria (20)

1987 ACR criteria (At least 4 out the 7 criteria are needed for the classification of RA)
1. Morning stiffness (at least one hour) (≥ 6 weeks)
2. Arthritis in three or more joints (≥ 6 weeks)
3. Hand joint arthritis (≥6 weeks)
4. Symmetric arthritis (≥ 6 weeks)
5. Rheumatoid nodules
6. Positive rheumatoid factor
7. Radiographic changes (erosions or juxta-articular decalcification in the hands and wrists)

Table 1.3 - 2010 ACR/EULAR criteria (19)

2010 ACR/EULAR criteria (≥ 6/10 required for a definitive classification of RA	
1. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (+/- involvement of large joints)	2
4-10 small joints (+/- involvement of large joints)	3
>10 joints (at least one small joint)	5
2. Serology	
Negative RF and negative ACPA	0
Low positive RF or ACPA (≤3 x upper limit of normal)	2
High positive RF or ACPA (>3x upper limit of normal)	3
3. Acute phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
4. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

1.2.8 Treatment

1.2.8.1 Principles of management

Several principles including disease severity, response to medication and comorbid conditions govern the treatment of RA. Treatment encompasses pharmacological and non-pharmacological interventions (21). The treatment of RA has increasingly focused on early diagnosis and intervention. This is of importance to relieve symptoms, prevent damage and preserve function. Non-pharmacological interventions are largely aimed at improving functionality, quality of life and alleviating pain. They include occupational therapy, psychological support, education, functional aids and lifestyle modifications.

Pharmacological treatment includes the early use of DMARDS. Glucocorticoids and nonsteroidal anti inflammatory drugs (NSAIDs) are used for initial symptomatic relief, adjunctive treatment in difficult to control patients, when changing DMARDs and with flares of disease (21).

1.2.8.2 Disease modifying anti-rheumatic drugs

Disease modifying anti-rheumatic drugs are comprised of two broad categories of agents, namely synthetic DMARDs and biological DMARDs. Synthetic agents include methotrexate, sulfasalazine, leflunomide and antimalarials. Biologic agents include TNF inhibitors (TNFi)(etanercept, adalimumab, infliximab), IL-6 receptor antagonists (tocilizumab), IL-1 antagonists (anakinra), anti-CD20 B cell antibodies (rituximab), T cell co-stimulation inhibitors (abatacept) and Jak inhibitors (tofacitinib)(21).

Synthetic DMARDs are the initial drugs of choice with their use being guided by disease severity and comorbid disease. Methotrexate is commonly used as initial treatment and is used in combination with other DMARDs in moderate to severe

disease. These drugs can be used in combination with other synthetic or biological agents in difficult to control disease (21).

1.2.8.3 Challenges to therapy

Due to the complex nature of the disease, various challenges are encountered in clinical practice. Some of these challenges are directly related to therapy. These include the side effect profile of medications, drug interactions and drug availability. This is particularly pertinent to the South African setting with resource and financial constraints. Biologic agents are costly and rarely available in the state health care sector in South Africa. They are often limited to use in clinical trials. In addition, the high burden of infectious diseases, especially tuberculosis, demands the judicious use of DMARDs.

1.3 Comorbidities in rheumatoid arthritis

1.3.1 Comorbidities in the industrialized world

Comorbidities are defined as diseases or disorders which occur in addition to the primary disease. They may occur incidentally, as a result of chronic inflammation or secondary to the physiological and psychological effects of the underlying disease process. In addition, they may develop as an indirect result of the treatment of RA. Comorbidities are common in RA patients in industrialized countries. In a United Kingdom (UK) study the baseline prevalence of one or more comorbidities in RA patients was 36% with a subsequent cumulative prevalence of 81% after 15 years (22). Patients with RA had on average 1.6 comorbidities with the number of comorbidities increasing with advancing age (22, 23). An Italian study showed that 78.6% of RA patients who were admitted to hospital had one or more comorbidities

(24). The high cumulative number and individual prevalence of comorbidities may be a reflection of improved survival and the late age of diagnosis.

A recent international cross sectional study evaluating comorbidities demonstrated a wide variation in their individual prevalence amongst differing nations (25). The study was carried out across 17 nations and demonstrated a high prevalence of depression, ischaemic cardiovascular disease, solid tumours and chronic obstructive pulmonary disease (COPD). This variability in the spectrum and prevalence of comorbid conditions is likely a reflection of genetic, ethnic and socioeconomic differences amongst nations. There is currently no local data on the prevalence of comorbidities in the South African rheumatoid population. Due to the high variability amongst differing nations, international data cannot necessarily be extrapolated to local populations.

1.3.2 Impact of comorbidities in rheumatoid arthritis

The impact of comorbidities in RA patients is multifaceted and should be carefully considered when managing the disease. The most drastic effect is the relationship between comorbidities and mortality. Comorbid diseases amongst RA patients increase mortality even after adjusting for other variables (22). With each additional comorbid condition, the risk of death increases. In established disease, numerous studies have shown an association between comorbidities and worsening levels of function and disability (22, 26, 27). Moreover, comorbidities have an economic impact. The overall expenditure on all forms of arthritis has increased in recent times. This, in part, can be attributed to the increase in the number of patients with comorbid conditions (28).

1.3.3 Charlson comorbidity score and index

Quantifying the burden of comorbidities is of value in both clinical and research settings. Various tools have been developed to aid in quantifying this burden. One such tool is the Charlson comorbidity score (CCS) and the Charlson comorbidity index/probability (CCI). The CCS is determined by adding assigned scores to various comorbidities as well as assigning a score for every decade above the age of 50 years. This cumulative score can be used to calculate the CCI which is a predictor of survival (29). The CCI has been validated for its ability to predict 10 year survival after adjusting for gender and disease states (30). It serves as an important research aid by quantifying comorbid disease thus allowing for comparisons to be drawn. Its clinical usefulness is in decision making of how aggressively to treat conditions in which various comorbidities coexist. The spectrum of comorbidities in RA is varied and for simplification can be grouped into the following systems: cardiovascular (CV), respiratory, psychiatric, infectious, malignancies, osteoporosis and gastrointestinal disease.

Table 1.4 - Charlson comorbidity score and index

Charlson comorbidity score and index	
Myocardial infarction (1 point)	COPD (1 point)
Congestive heart failure (1 point)	Peptic ulcer disease (1 point)
Liver disease: - Mild (1 point) - Moderate to severe (3 points)	Diabetes mellitus: Uncomplicated (1 point) Target organ damage (2 points)
Cerebrovascular disease (1 point)	Peripheral vascular disease (1 point)
Hemiplegia (2 points)	Dementia (1 point)
Moderate to severe renal disease (2 points)	Connective tissue disease - RA (1 point)
Leukaemia (2 points)	Lymphoma (2 points)
Solid tumor (2 points)	Metastatic disease (6 points)
AIDS (6 points)	
Age:	
0 - 49 years (0 points)	
50 - 59 years (1 point)	
60 - 69 years (2 points)	
70 - 79 years (3 points)	
80 - 89 years (4 points)	
90 - 99 years (5 points)	
100+ years (6 points)	
CCI: - $Y = e^{(ccs*0.9)}$ e = 2.71828 - $Z = 0.983^{Y}$ - Z = 10 year survival	
Legend: COPD - Chronic obstructive pulmonary disease AIDS – Acquired immune deficiency syndrome RA – Rheumatoid arthritis	

1.4 Specific comorbidities in rheumatoid arthritis

1.4.1 Ischaemic heart disease

Cardiovascular disease (CVD) has a marked impact on morbidity and is the most common cause of early mortality amongst RA patients in industrialized populations (31). The increase in CV related deaths in RA patients has been reported to be as high as sixty percent (32). Most of this risk is attributed to a twofold increased rate of myocardial infarction (MI)(33) with an increased likelihood of multi-vessel coronary

artery disease (CAD)(34). Silent MI and an increased risk of sudden cardiac death have also been reported (35). Despite advancements in treatment modalities and improved disease outcomes, mortality from CVD remains unchanged (32, 36). This highlights the need for an increased focus on CVD in RA in both clinical and research based settings.

Both traditional and non-traditional risk factors play a role in the pathogenesis of atherosclerotic disease in RA. Some traditional risk factors such as insulin resistance, obesity, reduced physical activity and smoking may be more prevalent in RA patients. In contrast, the evidence around the prevalence of other traditional risk factors such as dyslipidaemia, diabetes mellitus (DM) and hypertension is conflicting (37). Furthermore, the impact that these risk factors have differs amongst different ethnic groups. For example, in black Africans obesity is not related to atherosclerosis, whereas in African white women body mass index and waist to hip ratios are related to common carotid artery thickness and plaques (38). Traditional risk factors in isolation do not account for the extent of CVD in RA.

Endothelial dysfunction is postulated to play a significant role in atherosclerosis. The expression of adhesion molecules with subsequent monocyte adhesion accelerates and promotes atherosclerosis. Inflammatory mediators in RA such as C-reactive protein (CRP), IL-1 and TNF promote these adhesion molecules thereby enhancing atherosclerosis (39). Inflammatory mediators together with glucocorticoid use are associated with insulin resistance which further increases CV risk (37). Hypercoagulability mediated by fibrinogen, Von Willebrand factor, tissue factor and plasminogen activator inhibitor 1 also contribute to CAD in RA (40). In addition to the underlying inflammatory nature of the disease, drug therapy plays an integral role in the development of CVD in RA.

Glucocorticoid use for a period of more than 6 months at a medium dose, defined as an oral prednisone dose ≥7.5mg, is associated with a higher prevalence of hypertension (41). Glucocorticoid use at such doses are generally reserved for more severe disease however hypertension remains more prevalent even after adjusting for disease severity (41). The mechanism for this association is unclear and is thought to be multifactorial with increased arterial stiffness, increased vascular adrenergic sensitivity and renal mineralocorticoid effects playing a role. Selective cyclooxygenase 2 inhibitors and more recently non-selective NSAIDs, used to treat pain and inflammation in RA, have also been implicated in the development of hypertension and atherosclerotic disease through the inhibition of prostaglandins (42). Only methotrexate use is associated with a decreased CV mortality. This effect may be due to the protective anti inflammatory effect of the drug mediated through elevated adenosine levels (43). Treatment with TNFi has also been shown to improve endothelial dysfunction (44).

1.4.2 Heart failure

Rheumatoid arthritis is also associated with an increased risk for the development of congestive cardiac failure (CCF). A retrospective study showed a twofold increased risk of developing CCF amongst RA patients (45). Similar to CAD, this increased risk is thought to be multifactorial with traditional risk factors and drug therapy playing a role. This increased risk however, remains evident even after adjusting for traditional risk factors. Thus, mechanisms inherent to the underlying disease state are likely to be contributory. The link between heart failure and inflammation has been established. In RA, the effect of inflammation is further supported by the increased risk of heart failure seen in patients with elevated levels of IL-6, CRP and TNF (46).

1.4.3 Respiratory comorbidities

Respiratory comorbidities are a major cause of death in RA patients. Recent studies have shown that mortality related to respiratory disease is increased twofold in women with RA (47). This risk is even greater amongst women with RF positive disease.

Obstructive lung disease, in particular COPD, is more prevalent amongst American RA patients compared to the general population (48). The presence of obstructive lung disease in RA was associated with decreased survival rates. In the same study however, a decreased prevalence of asthma was noted amongst American RA patients. This is in contrast to a Taiwanese study which showed a significantly higher rate of asthma in RA (49). Although smoking may be more common amongst RA patients, obstructive lung disease occurs more frequently even after adjusting for smoking (48). T cell mediated responses are thought to play a role in respiratory disease. Smoking is thought to be a risk factor for the development of RA itself. Like CV comorbidities, the drugs used to treat RA have a significant impact on pulmonary disease.

Drug induced lung injury has various manifestations including an increased likelihood of infections, inflammatory lung disease and fibrotic lung disease. Methotrexate has been associated with the progression of subclinical interstitial lung disease (ILD)(50). In addition, its use may result in the development of an acute hypersensitivity pneumonitis, interstitial fibrosis (less commonly), asthma or an increase in the development of lung nodules. Leflunomide is associated with a higher risk of developing ILD and an increased risk of acute pneumonitis in those with pre-existing lung disease (51). It too, may lead to worsening pulmonary nodular disease. The use of sulfasalazine in RA has been associated with pneumonitis, nonspecific interstitial

pneumonia, pleural effusions and granulomatous lung disease (52). Biological agents used in the treatment of severe RA may improve pulmonary disease however some biological TNFi agents may rarely induce ILD (53).

1.4.4 Infections

Infections are one the three leading causes of death amongst RA patients. A higher incidence of serious or hospital requiring infections occur in RA patients. A twofold increased risk of serious infections is seen in RA compared to age matched non-RA patients (54). This is of particular concern amongst developing nations like South Africa with a high burden of infectious diseases such as HIV and tuberculosis (TB)(55). The increased risk of serious infections is likely a consequence of immune dysfunction, comorbid conditions and drug therapy.

Deficiencies in multiple components of the innate immune system may occur in RA patients. A neutropaenia can develop as a consequence of anti-neutrophil antibodies (56). In addition to a decrease in absolute neutrophil numbers, the neutrophils are functionally impaired with increased margination and apoptosis being observed (56). Gene mutations affecting complement factor 5 may also play a role in innate immune dysfunction. The adaptive immune system is also inept, thereby contributing to the increased risk of serious infections in RA. Thymic dysfunction as well as a decrease in the diversity of T cell receptors are seen in RA. This results in a subsequent decrease in the ability to recognize pathogenic antigens (57).

Comorbid conditions such as chronic lung disease, COPD, chronic kidney disease (CKD) and DM confer an increased risk to the development of infections. Other risk factors such as smoking and a higher degree of physical impairment are also contributory.

The use of glucocorticoids and other immunosuppressive therapies in the management of RA further impairs the immune system. Evidence relating to the susceptibility of developing infections with glucocorticoid use, points towards a dose dependent relationship. Doses of oral prednisone of >5mg/day are associated with a greater risk of infection (58, 59). Treatment with TNFi impairs immune response through the impaired activation of macrophages. Studies relating their use to the development of infections have shown various results. Randomized control trials have shown an increased risk for the development of serious infections with an odds ratio of 1.2 – 1.4. Observational studies however, have shown a decrease in the relative risk of serious infections over time (56). The development of TB is of particular concern with the use of TNFi. In contrast methotrexate confers a minimal risk to the development of serious infections (60). This is likely due to its immunosuppressive effects being offset by improved immune function achieved with control over inflammation.

1.4.5 Malignancy

The overall risk of malignancy in patients with RA remains unchanged compared to the general population. A site specific risk for malignancy is however seen. This risk is likely accounted for by a number of factors including underlying chronic inflammation, drug therapy, comorbid diseases and environmental factors. A meta-analysis of 21 publications demonstrated an increased risk of lymphoma and lung cancer amongst RA patients with a decrease in the incidence of colorectal and breast cancer (61).

The risk of lymphoma is increased twofold in RA with most of this risk accounted for by Hodgkin's lymphoma (61). Chronic inflammation, immune activation, decreased natural killer cell activity and decreased T suppressor lymphocyte activity is thought

to contribute to this increased risk. The risk of developing lung cancer in RA is increased by 1.5 to 3.5 times compared to the general population (61). Cigarette smoking is an established risk factor for the development of lung cancer, however the increased risk of lung cancer in RA persists even after adjusting for smoking (62). In addition inflammation and ILD are also contributing factors to the risk of malignancy (62).

The use of NSAIDs has a protective effect against the development of colorectal cancer and this effect may account for the reduced risk seen amongst RA patients (61). Azathioprine, methotrexate and alkylating agents may play a contributory role in developing malignancies especially lymphoma although evidence for this is uncertain (61). Furthermore, data regarding the risk of development of malignancies with the use of TNFi is contradictory. Several meta analyses have shown an increased risk of malignancy however observational studies have not demonstrated this same risk (61). The role of other confounding factors like chronic inflammation, comorbid diseases, severity of disease and other past or present medications make the pathogenic role of TNFi difficult to assess.

1.4.6 Gastrointestinal comorbidities

Gastrointestinal comorbidities in RA occur largely as a result of drug therapy with the most commonly implicated drug class being the NSAIDs. A wide spectrum of gastrointestinal diseases including gastritis, peptic ulcer disease (PUD), duodenal ulcers and oesphagitis are commonly seen amongst RA patients as a result of NSAIDs and glucocorticoid use. Patients affected with these conditions commonly present with dyspepsia, bleeding ulcers and/or perforation. Admissions with the above, although common, have decreased over time with admission rates of 0.5% in

the year 2000 (63). This is likely as a result of more judicious NSAIDs use as well as the use of proton pump inhibitors.

In addition to PUD, intestinal inflammation may also occur as a result of increased intestinal permeability with NSAID use. This may have a variety of clinical manifestations including intestinal perforations, bleeding and small bowel obstruction. Glucocorticoid use has also been associated with a higher rate of gastrointestinal perforations (64).

Hepatic dysfunction in RA patients may occur as a result of a drug induced hepatitis, autoimmune hepatitis, viral hepatitis or fatty liver disease. Viral based etiologies for the development of RA have been suggested with hepatitis B and C viruses being previously implicated in its pathogenesis (65). Maillefert et al have however, shown that the prevalence of hepatitis C in French RA patients (0.65%) was the same as in the general population (66). This finding suggests that the association between hepatitis C infection and RA is unlikely.

Hepatitis C may masquerade as RA by presenting with an arthritis thus posing a diagnostic challenge. Clifford et al have shown that a positive RF is seen in 76% of hepatitis C infected patients (67). The arthritis in hepatitis C infection is unlike RA in that it is a non-destructive, mono or oligoarthritis with a predisposition for large and medium sized joints. TNFi use in concomitant RA and hepatitis C does not seem to result in an increase in viral replication or worsening of disease (68).

Drug induced hepatic damage may also occur with a number of agents used in the treatment of RA. These agents include methotrexate, leflunomide, sulfasalazine and NSAIDs. As such, concomitant hepatic disease in RA patients calls for the judicious use of these drugs with regular careful monitoring for drug related liver toxicity.

1.4.7 Osteoporosis

Peri-articular osteoporosis (OP), seen radiologically, is a prominent feature of RA. In addition to localized bone loss, general bone loss occurs commonly (69). Osteoporosis increases the risk of fractures and vertebral deformities in these patients. The prevalence of OP, as well as its associated risk factors, varies widely amongst differing nations (70). Bone loss is attributed to a number of contributory factors. Underlying immune activation with subsequent cytokine and inflammatory mediator activation results in the differentiation and recruitment of osteoclasts. Osteoclast activity increases bone resorption resulting in OP. Gough et al demonstrated a relationship between higher CRP levels and increased bone loss thus suggesting a relationship between the degree of inflammation and bone loss (70). In further work done by Gough et al, early RA and higher disease activity were associated with a higher degree of bone mineral density (BMD) loss (71). Physical inactivity often as a result of severe disease with deformities and pain, also increases bone loss.

Osteoporosis is also influenced by drug therapy in RA patients. Glucocorticoid use impacts on bone mineral density with a higher cumulative glucocorticoid dose being related to a lower BMD (72). Other risk factors for bone loss include radiological evidence of RA damage, older age and a lower body mass index (72).

1.5 Summary

Comorbidities in RA patients are common in industrialized populations. A multitude of comorbidities are seen affecting a number of organ systems. Comorbidities are a function of a number of factors including chronic inflammation, genetics, environmental influences, socioeconomic dynamics and drug therapy. Comorbid

diseases have a significant impact on patient outcomes, disability, expenditure, drug therapy, morbidity and mortality. As a result of their diverse and complex aetiologies, comorbidities in RA patients vary widely with geographical location. Understanding the spectrum of local comorbidities, their prevalence, impact and associated risk factors facilitates patient management. It also aids in allocating sparse resources by determining which patients to screen and how aggressively to manage comorbid diseases.

1.6 Aims and objectives

This study aims to determine the frequency of comorbidities in black South Africans with RA. Furthermore, it aims to describe the relationship between comorbid diseases and their associated risk factors.

2. CHAPTER 2: PATIENTS AND METHODS

2.1 Patients

A retrospective record review of RA patients attending the Arthritis Clinic of the Chris Hani Baragwanath Academic Hospital (CHBAH) between 1988 - 2015 was undertaken. The CHBAH is a tertiary hospital located in Soweto and serves the indigent population residing in the south of Johannesburg. This population is heterogeneous and is largely comprised of the middle to lower income subgroup.

2.2 Criteria

The following criteria were used:

2.2.1 Inclusion criteria:

- Patients older than 18 years of age
- Patients fulfilling the 1987 (ACR) criteria for RA
- Patients with established disease, defined as a follow up duration of ≥5 years
- Black ethnicity, defined as all 4 grandparents being black South Africans

2.2.2 Exclusion criteria:

- Incomplete patient records

2.3 Methods

A convenient sample size of 500 patients were analyzed in the study. Patients were consecutively selected with records being kept in alphabetical order. Clinical data that was abstracted from the case records included:

- Demographics: Age at last follow up, gender, smoking and follow up duration
- Autoantibodies: RF and ACPA

- Extra-articular manifestations: Anaemia, nodulosis, scleritis, cutaneous vasculitis and ILD
- Comorbid diseases: Cardiovascular, CNS, respiratory, infections, gastrointestinal, malignancies and osteoporosis
- Drug therapy

Data was transcribed onto data collection sheets (Appendix A) and captured onto the electronic data collection tool REDCap (Research Electronic Data Capture).

2.4 Charlson comorbidity index

The CCS was used as a measure of the cumulative burden of comorbid diseases. The comorbidities captured as part of the CCS are illustrated in Table 1.4.

2.5 Definitions

ACR functional class (FC)(73):

1 – Able to perform self care, vocational and avocational activities.

2 – Avocational activities limited.

3 – Vocational and avocational limited.

4 – Limited self care, vocational and avocational activities.

Mild and severe disability was defined as a worst FC of 1-2 and 3-4 respectively. See appendix C for a full list of definitions.

2.6 Statistical analysis

Collected data was recorded, organized and analyzed using the following electronic aids: REDCap, Microsoft Office Excel 2007, MedCalc and STATISTICA version 12.

Normally distributed data (parametric data) were reported as means and standard deviations (SD). To compare categorical variables, the Pearson's chi square test was used, and where appropriate the two tailed Fisher's exact test was used. The Student's T-test was used to compare means between independent groups. Non-parametric data were expressed as medians and interquartile ranges (IQR). The Mann-Whitney test was used for non-parametric data.

3. CHAPTER 3: RESULTS

3.1 Demographics, clinical features and therapy

Table 3.1 depicts the demographics of the study population. Most patients were middle-aged to elderly females with long disease durations. The majority of patients tested were seropositive for either RF (91.0%) or ACPA (61.0%).

Most patients had severe disability at the time of diagnosis (50.5%). The median FC (worst) was 3.0 (IQR 2.0-3.0).

The commonest extra-articular manifestations (Table 3.2) are anaemia (78.2%) and subcutaneous nodules (31.0%). Other less common extra-articular features are scleritis, ILD and cutaneous vasculitis which were seen in 3.4%. 3.2% and 1.4% of patients respectively.

With respect to medical therapy the majority of patients in the study had a history of using NSAIDs (98.8%), methotrexate (95.4%), other DMARDs (93%) and oral prednisone (85.8%). A small percentage of patients were treated with biologic agents (rituximab 2.6% and TNFi 1.0%) and cyclophosphamide (2.2%).

Table 3.1 - Demographics, autoantibodies and functional class of the study population

Demographics	**Number**
Total number of patients	500
Age, mean years (±SD)	60.0 (11.1)
Female, (%)	435 (87)
Male, (%)	65 (13)
Female:Male	6.7:1.0
Follow up duration, mean years (±SD)	10.7 (5.0)
Symptom duration (prior to diagnosis), mean years (±SD)	5.1 (6.1)
Autoantibodies	**Number (%), total 500**
Rheumatoid factor	455 (91.0)
Anti-citrullinated peptide antibodies	305/376 (81.1)
Functional Class (ACR)	**Number (%), total 500**
Worst	
1	6 (1.2)
2	146 (29.2)
3	277 (55.4)
4	71 (14.2)
Mean (IQR)	3.0 (2.0 - 3.0)

Table 3.2 - Extra-articular disease and drug therapy

Extra-articular disease	**Number (%), total 500**
Anaemia: Current	194 (38.8)
Past history	197 (39.4)
Cumulative frequency	391 (78.2)
Nodulosis	155 (31.0)
Scleritis	17 (3.4)
Interstitial lung disease	16 (3.2)
Vasculitis	7 (1.4)
Drug therapy	**Number (%), total 500**
History of non steroidal anti inflammatory drugs	494 (98.8)
History of methotrexate	477 (95.4)
Other non-biological disease modifying drugs	465 (93.0)
History of prednisone	429 (85.8)
Rituximab	13 (2.6)
Cyclophosphamide	11 (2.2)
TNFi	5 (1.0)

3.2 Comorbidities

Comorbidities occurred commonly in the study population with 98.0% of all patients having one or more comorbid diseases. The median number of comorbidities was 3.0 (IQR 2.0 - 4.0). The median CCS was 3.0 (IQR 2.0 - 4.0) and when adjusted for age was 1.0 (IQR 1.0 - 2.0). This equated to a median 10 year survival rate of 77.0% (IQR 53.0% - 90.0%). Table 3.3 describes the frequency in which individual comorbid diseases occurred in the study population. Hypertension, hypercholesterolaemia, PUD, osteoporosis and serious infections were the most frequently occurring comorbid diseases.

Table 3.3 - Frequency of comorbidities

Comorbidity	Number (%), total 500	Comorbidity	Number (%), total 500
Gastro Intestinal:		**Other:**	
Peptic Ulcer Disease	73/114 (64.0)	Moderate/Severe Renal Failure	33 (6.6)
Liver Disease: Mild	11 (2.2)		
Moderate/Severe	0	**Non CCS comorbidities:**	
		Hypertension	350 (70.0)
Cardiovascular/CNS:		Hypercholesterolaemia	221/466 (47.4)
Diabetes Mellitus	77 (15.4)	Osteoporosis	62/132 (47.0)
Congestive Heart Failure	33 (6.6)	Serious Infections	56 (11.2)
Cerebrovascular disease	14 (2.8)	Tuberculosis	53 (10.6)
Hemiplegia	7 (1.4)	HIV	44/472 (9.3)
Peripheral Vascular Disease	3 (0.6)	History of Fractures	39 (7.8)
Coronary Artery Disease	3 (0.6)	Asthma	24 (4.8)
		Hypothyroidism	13/459 (2.8)
Respiratory:		Malignancy	9 (1.8)
COPD	7 (1.4)	Hepatitis: B	4/372 (1.1)
		C	6/372 (1.6)
Infections:		Hyperthyroidism	3/459 (0.7)
AIDS	3/472 (0.6)		

3.2.1 Cardiovascular comorbidities

Table 3.3 depicts the frequencies of cardiac comorbidities. A history of cigarette smoking was documented. A total of 20.8% (82/395) had a history of cigarette smoking. Of all the male patients studied 55.4% (36/65) had a history of cigarette smoking. In contrast only 10.6% (46/435) of females had a smoking history. Hypertension, hypercholesterolaemia and DM were found frequently. Despite the high frequency of CV risk factors, CAD was uncommon with a prevalence of 0.6%.

3.2.2 Gastrointestinal comorbidities

Only patients with clinically suspected PUD had undergone a gastroscopy (G-scope). Of the 114 patients who had undergone a G-Scope the majority (64.0%) had a proven diagnosis of PUD. Liver disease was an uncommon finding in the study.

3.2.3 Osteoporosis

DEXA scans were done in those clinically suspected of having OP. Amongst the 132 patients who had DEXA scans, OP was a common finding (47.0%).

3.2.4 Serious infections

Serious infections occurred commonly in the study population (11.2%). TB was noticeably prevalent with 53 patients (10.6%) having had the disease. Of note, none of these patients had been treated with TNFi. AIDS defining illnesses were uncommon in the HIV positive population.

3.2.5 Respiratory comorbidities

Non-infectious respiratory comorbidities like asthma, ILD and COPD were seen in 4.8%, 3.2% and 1.4% of the population respectively. Amongst the patients diagnosed with COPD, 6 had a history of cigarette smoking and 5 were males (71.4%). The exact etiology and pattern of ILD amongst these patients was not explored.

3.2.6 Malignancies

The following malignancies were documented:

- Cervical carcinoma (3 patients)
- Breast carcinoma (3 patients)
- Prostate carcinoma
- Renal cell carcinoma
- Multiple myeloma

Of note no lymphomas were recorded.

3.3 Predictors of comorbidities

Both increasing age (Figure 3.1) and a longer length of patient follow up was associated with a significant increase in the total number of comorbidities (p value <0.001 for both variables). In addition to age and length of follow up, disability was a function of the total number of comorbidities (Table 3.4). Of note, there was no relationship between markers of severe disease (seropositive disease, prednisone use and nodulosis) and the total number of comorbidities.

Table 3.4 - Predictors of comorbidities

	Median number of comorbidities (IQR)	P value (Mann-Whitney test)
Disability:		
- Mild	2.00 (2.00 - 3.00)	<0.001
- Severe	3.00 (2.00 - 4.00)	
Autoantibodies		
RF: - Positive	- 3.00 (2.00 - 4.00)	0.603
- Negative	- 3.00 (2.00 - 4.00)	
ACPA: - Positive	- 3.00 (2.00 - 4.00)	0.220
- Negative	- 3.00 (2.00 - 4.00)	
Prednisone use:		
- Present	- 3.00 (2.00 - 4.00)	0.952
- Absent	- 3.00 (2.00 - 4.00)	
Nodulosis:		
- Present	- 3.00 (2.00 - 4.00)	0.236
- Absent	- 3.00 (2.00 - 4.00)	

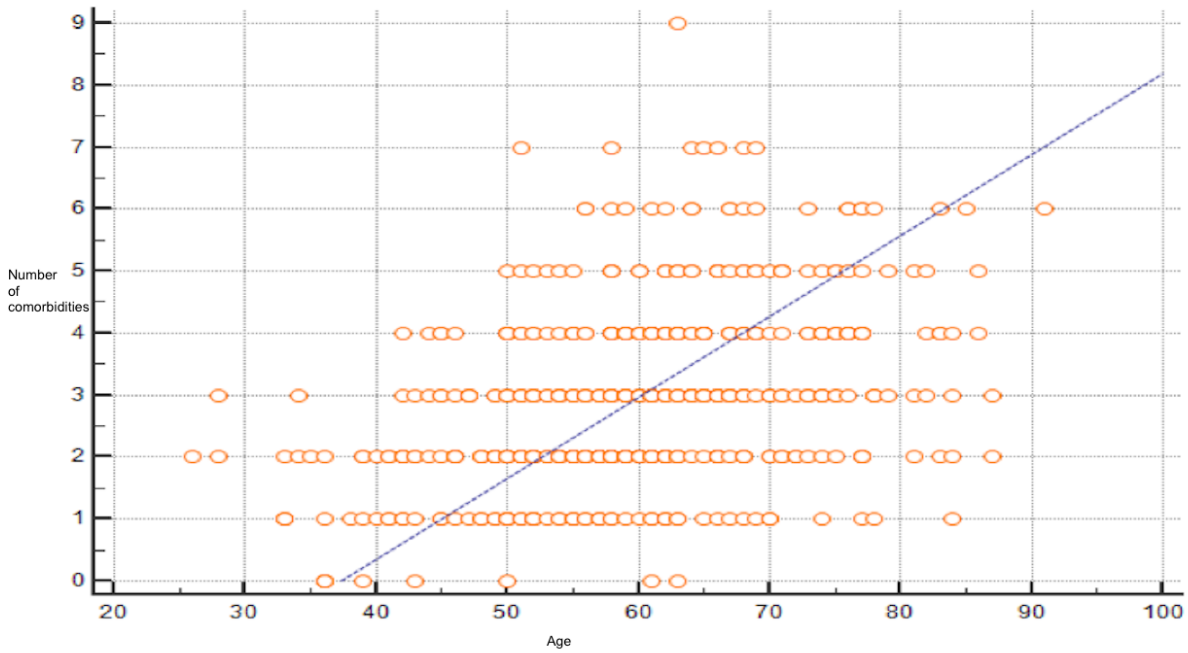

Figure 3.1 - Scatter diagram depicting age and number of comorbidities

3.3.1 Disability and comorbidities

Table 3.5 illustrates the comorbidities which were significantly associated with severe disability. Patients with markers of disease severity including a history of arthroplasty, rheumatoid nodules or prednisone use, were more likely to have severe disability. Furthermore, the relationship between ACPA positivity and disability as well as a history of scleritis and disability approached statistical significance with p values of 0.057 and 0.089 respectively.

Table 3.5 – Relationship between disability and comorbid diseases

	ACR1-2, n (%)	ACR3-4, n (%)	Odds Ratio (95% CI)	P value (Fisher's exact)
Arthroplasty	7/152 (4.6)	66/348 (19.0)	4.85 (2.17 - 10.84)	<0.001
CCF	4/152 (2.6)	29/348 (8.3)	3.36 (1.16 - 9.74)	0.018
Osteoporosis	9/152 (5.9)	53/348 (15.2)	2.52 (1.06 - 6.04)	0.039
Serious infections	9/152 (5.9)	47/348 (13.5)	2.48 (1.18 - 5.20)	0.013
Prednisone use	118/152 (77.6)	311/348 (89.4)	2.42 (1.45 - 4.04)	<0.001
History of anaemia	104/152 (68.4)	287/348 (82.5)	2.17 (1.4 - 3.37)	<0.001
Nodulosis	34/152 (22.4)	121/348 (34.8)	1.85 (1.19 - 2.87)	0.006
Hypertension	96/152 (63.2)	254/348 (73.0)	1.58 (1.05 - 2.37)	0.034

3.3.2 Associations with serious infections

As noted in Table 3.6, patients with osteoporosis, vasculitis, anaemia, HIV, arthroplasty and longer disease durations were more likely to have had serious infections.

Table 3.6 – Relationship between serious infections and comorbid diseases

	Patients with serious infections, n (%)	Odds Ratio (95% CI)	P value (Fisher's exact)
Osteoporosis: - Present - Absent	- 15/62 (24.2) - 4/70 (5.7)	4.23 (1.48 – 12.08)	0.003
Vasculitis: - Present - Absent	- 3/7 (42.9) - 53/493 (10.8)	4.00 (1.63 – 9.73)	0.034
History of anaemia: - Present - Absent	- 52/391 (13.3) - 4/109 (3.7)	3.62 (1.34 – 9.80)	0.005
HIV status: - Positive - Negative	- 10/44 (22.7) - 42/428 (9.0)	2.32 (1.25 – 4.29)	0.014
Athroplasty: - Present - Absent	- 15/73 (20.5) - 41/427 (9.6)	2.14 (1.25 – 3.66)	0.009
Disease duration: - >10 years - ≤10 years	- 34/213 (16.0) - 22/287 (7.7)	2.08 (1.26 – 3.45)	0.004

3.3.3 Associations with osteoporosis

Patients who were diagnosed with OP were more likely to have had arthroplasty surgery than those without OP (prevalence of 30.6% and 10.0% respectively, Fischer's exact two tailed p value of 0.013).

3.4 Mortality

There were 37 confirmed deaths noted in the study population during their follow up period. As depicted in Table 3.7, the deceased population had a high mean age and follow up duration (64.0 and 12.3 years respectively). Furthermore, the deceased

population had a significantly higher number of comorbidities (median of 4.0 [IQR 3.0 - 5.0] vs 3.0 [IQR 2.0 - 4.0], Mann-Whitney p value <0.001) and a significantly higher FC than the living population (median 4.0 [IQR 3.0 - 4.0] vs 3.0 [IQR 2.0 - 3.0], Mann-Whitney p value <0.001). The CCI was significantly higher amongst the deceased as compared to the living (median of 0.77 [IQR 0.53 - 0.90] vs 0.21 [IQR 0.15 - 0.59], Mann-Whitney p value <0.001), thus validating its clinical utility to predict mortality. The most common comorbidities amongst the deceased were PUD, anaemia, hypertension and serious infections. Although the exact causes of death were not confirmed by means of an autopsy, patient records were used to determine the most probable cause of death in 17 patients (see Table 3.8).

Table 3.7– Demographics, autoantibodies, functional class and comorbidities amongst the deceased

Demographics	**Number**
Total number of patients	37
Age at last visit, mean years ±SD	64.0 (10.7)
Female, (%)	29 (78.4)
Male, (%)	8 (21.6)
Follow up duration, mean years (±SD)	12.3 (5.6)
Symptom duration (prior to diagnosis), mean years (±SD)	5.1 (6.1)
Autoantibodies	**Number (%)**
RF	34 (91.9)
ACCP	7/10 (70.0)
Functional Class (worst)	**Number**
Functional class, median (IQR)	4.0 (3.0 - 4.0)
Comorbidities	**Number**
Number of comorbidities, mean ±SD	4.0 (1.5)
CCS (age adjusted), mean ±SD	3.0 (1.5)
PUD, n (%)	13/14 (92.9)
Anaemia, n (%)	34 (91.9)
Hypertension, n (%)	26 (70.3)
Serious infections, n (%)	15 (40.5)
Arthroplasty, n (%)	12 (32.4)
CCF, n (%)	10 (27.0)
Tuberculosis, n (%)	9 (21.6)
Fractures, n (%)	6 (16.2)
Malignancy, n (%)	2 (5.4)

Table 3.8 Causes of death

Sepsis: - Pulmonary TB - TB with a drug induced liver injury - Community acquired pneumonia - Nosocomial pneumonia - Septicaemia - Colonic perforation with intra-abdominal sepsis	Pulmonary embolism
	Cervical cancer
	CCF
	Post TB bronchiectasis with decompensated cor-pulmonale
	COPD with decompensated cor-pulmonale
	ILD

3.4.1 Comorbidities amongst the deceased

Congestive cardiac failure, serious infections, ILD, arthroplasty, TB and PUD was more common amongst those who have demised during follow up (Table 3.9). In addition, more patients with a prior history of arthroplasty had demised.

Table 3.9 – Common comorbidities and clinical features amongst the deceased

	Alive, number (%) Total 463	**Deceased, number (%) Total 37**	**Odds ratio (95% CI)**	**P value (Fisher's exact)**
CCF	23 (5.0)	10 (27.0)	5.44 (2.80 – 10.55)	<0.001
Serious infections	41 (8.9)	15 (40.5)	4.58 (2.81- 7.45)	<0.001
ILD	16 (3.5)	5 (13.5)	3.91 (1.51 – 10.08)	0.014
Arthroplasty	61 (13.2)	12 (32.4)	2.46 (1.46 – 4.14)	0.003
TB	45 (9.7)	8 (21.6)	2.22 (1.13 – 4.36)	0.031
PUD	60/100 (60.0)	13/14 (92.9)	1.54 (1.24 – 1.92)	0.012

4. Chapter 4: Discussion

4.1 Demographic profile of black South African rheumatoid arthritis patients

Rheumatoid arthritis occurs more commonly in females, amongst black South Africans. The female predominance noted in this study was larger than that described previously with a female to male ratio of 6.7:1. Even at presentation, the majority of patients had severe disability. This is in contradiction to earlier SA data demonstrating a milder course of the disease (3). Severe disability at presentation is possibly a consequence of the delay in seeking health care and a reflection of the barriers to accessing specialized health care in South Africa. On average, patients presented to the rheumatology department after being symptomatic for 5.13 years. Barriers to accessing health care include socioeconomic difficulties, as well as a lack of health care facilities and infrastructure. Addressing these barriers are important to ensure early treatment with DMARDs and thus preventing disability.

4.2 Comorbidities in black South African rheumatoid arthritis patients

Comorbidities in black South African RA patients are common with 98% of all patients having had one or more comorbid conditions. This is higher than that seen in European nations like the UK and Italy (78.6%)(24). Over a period of 15 years, Sam Norton (22) demonstrated in 2012 that 81% of RA patients in the UK had one or more comorbid conditions. Furthermore, not only are comorbidities more prevalent in black South African RA patients, but these patients also have a higher total number of comorbid illnesses. The median number of comorbidities in the study population equaled to 3.00 per patient. In comparison, in industrialized populations the median number of comorbidities equaled to 1.60 (22, 23). The high number of comorbid conditions seen in black SA patients is possibly a consequence of multiple factors

including poor socioeconomic conditions, limited access to health care facilities, delayed presentations, a high burden of infectious diseases, the frequent use of NSAIDs and glucocorticoids. Comorbid diseases worsen disability, increase mortality and increase economic expenditure (22, 26, 27). It is therefore vital for local treating physicians to place emphasis on, screen for and appropriately manage comorbid diseases in RA.

4.2.1 Cardiovascular disease

Hypertension was commonly seen occurring with a frequency of 70.0% (350/500). This is higher than that described in other industrialized nations and black non RA South Africans (25, 74, 75). A 2014 multi centric international cross sectional study by Dougados et al. (25) showed that hypertension occurred with a prevalence of 39.0% (156/400) and 34.9% (15/43) in the USA and UK respectively. In that study the highest prevalence of hypertension was found in Hungary and Uruguay with a prevalence of 57.0% each.

In addition to hypertension, a diagnosis of DM was common in the study population, occurring with a prevalence of 15.4% (77/500). In comparison, DM occurred with a frequency of 21.0% and 7.0% in USA and UK respectively (25).

Hypercholesterolaemia was commonly found amongst black SA patients (47.4%, 221/466). With regards to cigarette smoking, 20.8% (82/395) of patients had a history of cigarette smoking (past or present). This is lower than that described in first world countries with the prevalence of current cigarette smokers being 23% in both the USA and UK.

Of the 500 patients studied, only 3 (0.6%) had a history of CAD. In comparison CAD occurred with frequencies of 5% and 2% in the USA and UK respectively (25).

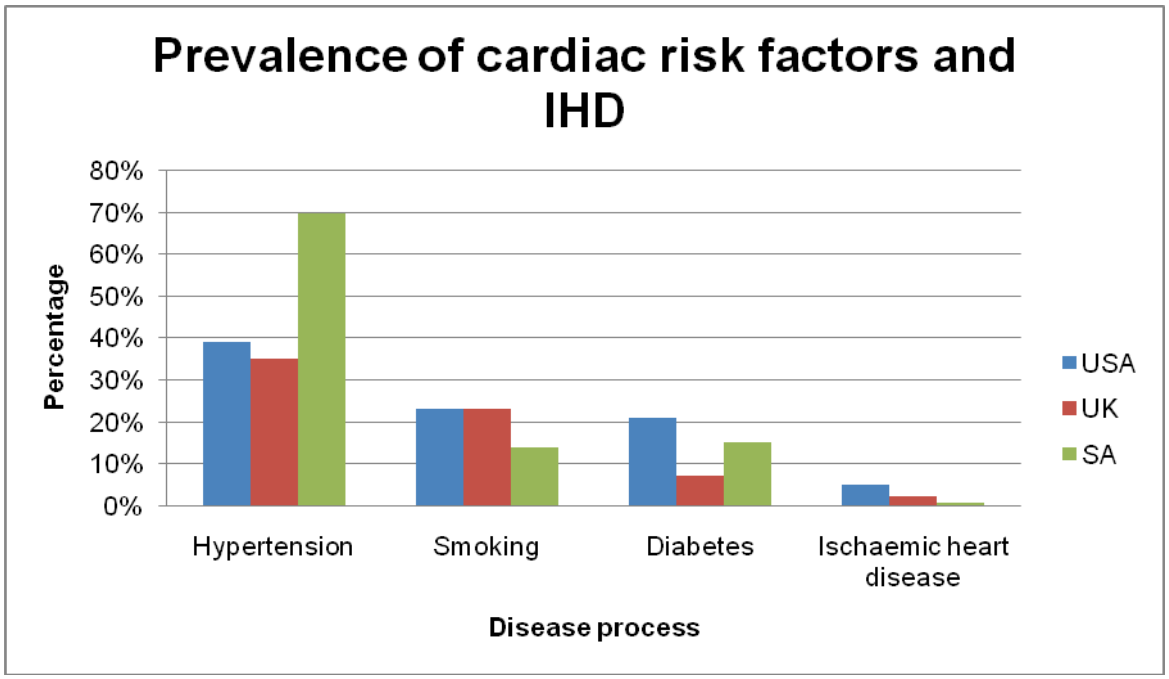

Figure 4.1 – The geographical prevalence of cardiac risk factors and CAD

Furthermore, the prevalence of cardiac risk factors differs between RA patients and the baseline non-RA black South African population (Figure 4.2). The non-RA data in this figure was extracted from black patients in the Heart of Soweto registry and studies carried out by Silwa K, et al (74, 75). These figures were based on a population referred to a specialized cardiac unit and are therefore likely to be an over estimate of the true burden of CVD and CV risk factors in South African patients. In addition, hypercholesterolaemia was defined as a total cholesterol value of >4.5mmol/l in this study. Despite this over estimation, the prevalence of hypercholesterolaemia and DM was still higher amongst the black RA population with non-RA figures in black patients equaling 39% and 9% for hypercholesterolaemia and DM respectively. The prevalence of hypertension amongst black females was 61.9% (74). Given the above, the prevalence of CAD paradoxically remained lower in black RA patients (0.6%) as opposed to black non-RA South Africans (10.0%).

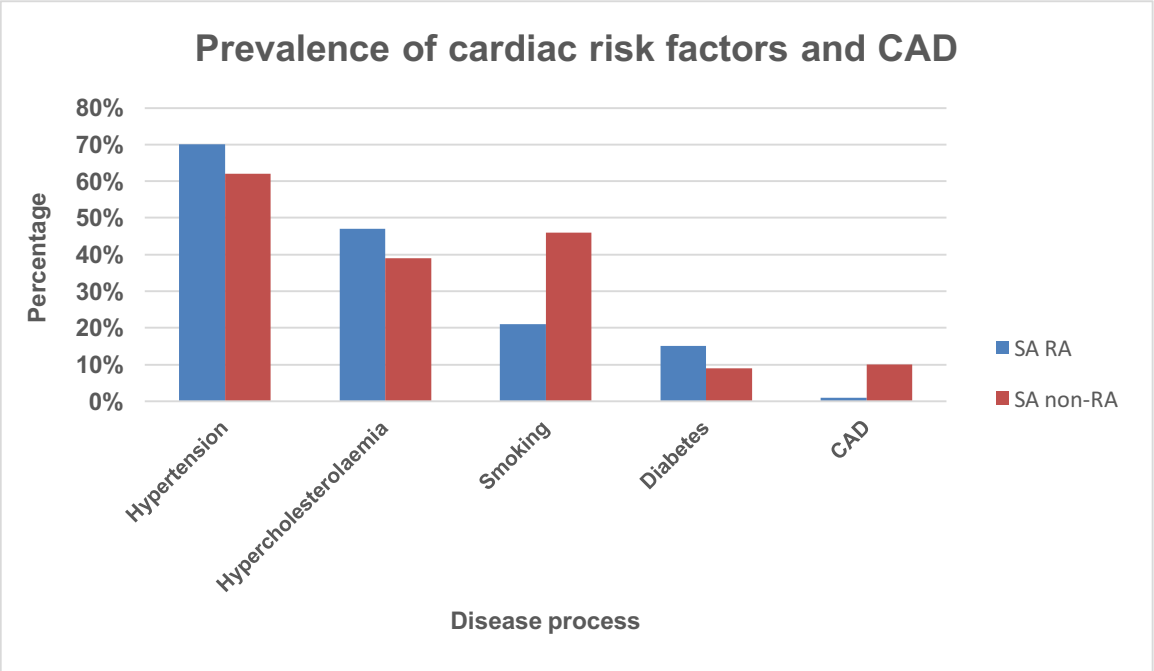

Figure 4.2 – The prevalence of cardiac risk factors and CAD amongst RA and non RA South Africans (74, 75)

The underlying mechanism for the high prevalence of hypertension amongst black RA patients remains illusive. The common use of NSAIDs (98.8%) and glucocorticoids (85.8%) may be a possible contributory factor to the development of hypertension. Furthermore, the low prevalence of CAD in black South African RA patients suggests that some degree of protection is conferred in this population. The exact nature of this protective relationship is unknown and may be influenced by a combination of disease process itself, genetics, lower levels of central obesity and lower levels of systemic IL-6 (76). More research is needed to better define this relationship.

4.2.2 Osteoporosis

Osteoporosis occurred commonly (42%, 62/132). Performing DEXA scans on all RA patients in developing nations is challenging considering financial and other resource constraints. Undiagnosed and untreated, OP increases the likelihood of

complications like fragility fractures and the need for arthroplasty amongst patients with OP (see section 3.3.3). Thus, undiagnosed OP has both financial implications as well as an impact on morbidity, mortality and quality of life. These costs may offset the costs of performing DEXA scans. It is thus prudent to allocate resources efficiently and as such further data is needed amongst local RA patients to help identify those at risk and those needing further screening.

4.2.3 Serious infections

Serious infections occur commonly amongst RA patients (11.2%, 56/500) and are significantly more common in HIV positive patients. Tuberculosis is of particular concern in the local South African setting. Patients with OP, vasculitis, anaemia, HIV, orthopaedic surgery and longer disease durations, are at a higher risk of developing serious infections. As a result, these patients should be monitored more closely. The burden of infectious diseases is further amplified by the use of immunosuppressive agents and biologic DMARDs. Treating clinicians should thus individualize treatment by weighing the benefits of therapy with local infection risk profiles. Further local data will assist in facilitating this therapeutic decision making process.

4.3 Mortality

In our study population, mortality was found to be a function of age, severity of disability and the number of comorbid diseases. This further illustrates the importance of screening for and appropriately managing comorbidities in RA patients. A history of CCF, serious infections and ILD conferred the highest risk of mortality amongst black South African RA patients. This is similar to that seen in industrialized countries. Data from the UK by Ogdie et al has shown that CVD,

respiratory disease, malignancies and infections were the most common causes of death (77).

4.4 Limitations

The inherent retrospective nature of the study means that the accuracy is reliant on availability of data in patient's files. Incomplete, missing or inaccurately completed files affect the quality of data. The extents to which comorbidities are investigated for by attending clinicians also limit the quality of the data. Most comorbid conditions are investigated for, on the basis of clinical suspicion and not on the basis of routine screening thus resulting in the under diagnosis of comorbid conditions.

The high prevalence of anaemia in the study population may have influenced HbA1c values thus affecting the true prevalence of DM. With regards to OP, the influence of hyperparathyroidism was not accounted for.

Post mortem autopsies were not carried out on deceased patients, thus the cause of death could not be determined with certainty. The causes of death amongst patients were the most likely or presumptive cause of death. The impact of terminal events and diseases were therefore not accurately determined.

5. Chapter 5: Conclusion

Comorbidities in black South African RA patients are common with a high average number of comorbidities seen. The spectrum of comorbid diseases varies geographically. This holds true amongst black SA patients in which a unique comorbid disease profile exists. Hypertension occurs commonly amongst these patients. Its precise etiology however, remains unknown. In addition to hypertension, other cardiac comorbidities and risk factors are also common. Despite this, the prevalence of CAD still remains low. The exact protective mechanism against CAD is unknown.

South African clinicians face unique challenges in the management of RA. The high burden of serious infections needs to be considered in the management of patients with particular regards to immunosuppressive therapy. Resource limitations demand the efficient and appropriate use of available investigative tools. Thus data concerned with comorbid diseases assists in identifying patients at risk and facilitates the efficient allocation of scarce resources. The common finding of osteoporosis amongst the study population suggests that more intensive screening should be considered in RA patients. Despite its limitations (section 4.4), this study is to our knowledge the largest cohort undertaken to investigate comorbid diseases in black South African RA patients.

Appendix A – Data collection sheet (established using REDCap)

Demographics

Patient number _____

Gender
◯ Male
◯ Female

Age _____

Disease duration since diagnosis (years) _____

Duration of symptoms prior to diagnosis (years) _____

Rheumatoid factor
◯ Positive
◯ Negative
◯ Unknown

Anti CCP
◯ Positive
◯ Negative
◯ Unknown

Extra articular disease
☐ Nodulosis
☐ Vasculitis
☐ Sclerosis

Status
◯ Alive
◯ Deceased
◯ Unknown

Cause of death _____

Risk Factors

Patient number _____

Hypertension
◯ Yes
◯ No

Diabetes Mellitus
◯ Yes
◯ No

Target organ damage
◯ Yes
◯ No

Dyslipidaemia
◯ Yes
◯ No

Smoking
◯ Never
◯ Ever
◯ Present

Functional class at presentation _____

Worst functional class _____

Orthopaedic surgery

- ☐ None
- ☐ Soft tissue
- ☐ Arthroplasty

History of fractures

- ◯ Yes
- ◯ No

Moderate to severe kidney disease

- ◯ Yes
- ◯ No

Hyperthyroidism

- ◯ Yes
- ◯ No

Hypothyroidism

- ◯ Yes
- ◯ No

Dementia

- ◯ Yes
- ◯ No

Anaemia

- ◯ Never
- ◯ Ever
- ◯ Present

Charlson comobidity score _____

Charlson comorbidity index _____

Comorbidities

Patient number _____

Cardiovascular

Ischaemic heart disease

- ◯ Yes
- ◯ No

Congestive heart failure

- ◯ Yes
- ◯ No

Peripheral vascular disease

- ◯ Yes
- ◯ No

Cerebrovascular disease

- ◯ Yes
- ◯ No

Hemiplegia

- ◯ Yes
- ◯ No

Gastrointestinal

Peptic ulcer disease

- ◯ Yes
- ◯ No

Liver disease

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe

Respiratory

Interstitial lung disease
- ◯ Yes
- ◯ No

COPD
- ◯ Yes
- ◯ No

Asthma
- ◯ Yes
- ◯ No

Infections

HIV
- ◯ Yes
- ◯ No
- ◯ Unknown

AIDS
- ◯ Yes
- ◯ No

TB
- ◯ Yes
- ◯ No

Hepatitis
- ☐ A
- ☐ B
- ☐ C
- ☐ None

Severe infections
- ◯ Yes
- ◯ No

Malignancies

Lymphoma
- ◯ Yes
- ◯ No

Leukaemia
- ◯ Yes
- ◯ No

Lung Cancer
- ◯ Yes
- ◯ No

Other solid tumors _____

Metastatic disease
- ◯ Yes
- ◯ No

Skeletal

Osteoporosis
- ◯ Yes
- ◯ No

Appendix B – Definitions

Cardiovascular risk factors:

- Hypertension: systolic blood pressure of ≥140mmHg or a diastolic blood pressure of ≥90mmHg or on antihypertensive medication (78).
- Diabetes Mellitus: fasting glucose level of ≥7mmol/l, a glycated haemoglobin A1c of ≥6.5%, a random plasma glucose of ≥11.1mmol/l with symptoms or already on an oral hypoglycaemic agent or insulin (79).
- Hypercholesterolaemia: A total cholesterol level of ≥5.0mmol/l.

Cardiovascular disease:

- Myocardial infarction: Patients with one or more definite or probable events defined as a hospitalization for chest pain with electrocardiographic and/or enzyme changes (29).
- Congestive cardiac failure: Patients with exertional dyspnea or paroxysmal nocturnal dyspnea who have responded symptomatically or clinically to treatment (29).
- Peripheral vascular disease: A history of intermittent claudication, bypass surgery for arterial insufficiency, gangrene, acute arterial insufficiency, thoracic aneurysm or abdominal aneurysm (29).
- Cerebrovascular disease: A history of a haemorrhagic or ischaemic stroke with minor or no residual weakness or a transient ischaemic attack (29).
- Hemiplegia: Hemiplegia or paraplegia as a result of a cerebrovascular accident or other pathology (29).

Anaemia:

- Males – Haemoglobin level of <14.3g/dL (based on local laboratory reference values).

- Females – Haemoglobin level of <12.1g/dL (based on local laboratory reference values).

Osteoporosis: A DEXA T-score of less than -2.5 SD (80).

Moderate to severe kidney disease: Defined by a glomerular filtration rate (GFR) of ≤60mL/min/1.73m² or patients on dialysis, those who have had a kidney transplant and those with uraemia (81).

Serious infections: Any infection requiring hospital admission or intravenous antibiotic therapy.

Gastrointestinal:

- Peptic ulcer disease and gastritis: Based on gastroscopic evidence of disease.
- Liver disease: Mild liver disease includes chronic infection with hepatitis B or C or cirrhosis without evidence of portal hypertension. Moderate liver disease includes cirrhosis with portal hypertension (non-variceal bleeding). Severe liver disease consists of ascites, jaundice, portal hypertension, variceal bleeds or a liver transplant (29).

Pulmonary disease:

- COPD: the presence of compatible symptoms and spirometry showing airflow limitation (a forced expiratory volume after 1 second / Forced vital capacity (FVC) ratio of <0.7 and a FEV1 of <80% of predicted) (82).
- Asthma: A history of intermittent typical symptoms, demonstration of variable airflow limitation by spirometry and exclusion of alternative diagnoses.

Malignancies: Any solid or haematological cancer will be recorded.

Dementia: Patients with moderate to severe cognitive deficit with impaired function from any cause (29).

Appendix C – Ethics clearance form

R14/49 Dr Vikash Goolab Lala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140882

NAME: (Principal Investigator)	Dr Vikash Goolab Lala
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Co Morbidities in Black South Africans with Rheumatoid Arthritis
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr N Govind
APPROVED BY:	Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/09/2014

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

References

1. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. The Lancet. 376(9746):1094-108.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis and Rheumatism. 2008;58(1):26-35.
3. Anderson IF. Rheumatoid arthritis in the Bantu. South African Medical Journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1970;44(43):1227-9.
4. Meyers OL, Daynes G, Beighton P. Rheumatoid arthritis in a tribal Xhosa population in the Transkei, Southern Africa. Annals of the Rheumatic Diseases. 1977;36(1):62-5.
5. Solomon L, Robin G, Valkenburg HA. Rheumatoid arthritis in an urban South African Negro population. Annals of the Rheumatic Diseases. 1975;34(2):128-35.
6. Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY. Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis. Journal of Global Health. 2012;2(2):020406.
7. Weyand CM, Hicok KC, Conn DL, Goronzy JJ. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Annals of Internal Medicine. 1992;117(10):801-6.
8. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. British Journal of Rheumatology. 1993;32(10):903-7.
9. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis and Rheumatism. 2006;54(1):38-46.
10. Wu X, He B, Liu J, Feng H, Ma Y, Li D, et al. Molecular Insight into Gut Microbiota and Rheumatoid Arthritis. International Journal of Molecular Sciences. 2016;17(3).
11. Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for rheumatoid arthritis. Current Opinion in Rheumatology. 2009;21(3):279-83.
12. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
13. Sudoł-Szopińska I. Rheumatoid arthritis: what do MRI and ultrasound show. Journal of Ultrasonography. 2017;17(68):5-16.
14. Patil P, Dasgupta B. Role of diagnostic ultrasound in the assessment of musculoskeletal diseases. Therapeutic Advances in Musculoskeletal Disease. 2012;4(5):341-55.
15. Bhasin S, Cheung PP. The Role of Power Doppler Ultrasonography as Disease Activity Marker in Rheumatoid Arthritis. Disease Markers. 2015;2015:9.
16. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Annals of the Rheumatic Diseases. 2003;62(8):722-7.
17. Turesson C, Schaid DJ, Weyand CM, Jacobsson LT, Goronzy JJ, Petersson IF, et al. Association of HLA-C3 and smoking with vasculitis in patients with rheumatoid arthritis. Arthritis and Rheumatism. 2006;54(9):2776-83.
18. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. The Journal of Rheumatology. 2002;29(1):62-7.
19. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and Rheumatism. 2010;62(9):2569-81.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and Rheumatism. 1988;31(3):315-24.

21. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Annals of the Rheumatic Diseases. 2017.
22. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology. 2013;52(1):99-110.
23. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11(3):229.
24. Parodi M, Bensi L, Maio T, Mela GS, Cimmino MA. Comorbidities in rheumatoid arthritis: analysis of hospital discharge records. Reumatismo. 2005;57(3):154-60.
25. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Annals of the Rheumatic Diseases. 2014;73(1):62-8.
26. Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010;69(3):536-41.
27. van den Hoek J, Roorda LD, Boshuizen HC, van Hees J, Rupp I, Tijhuis GJ, et al. Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study. Arthritis Care & Research. 2013;65(7):1157-65.
28. Cisternas MG, Murphy LB, Yelin EH, Foreman AJ, Pasta DJ, Helmick CG. Trends in medical care expenditures of US adults with arthritis and other rheumatic conditions 1997 to 2005. The Journal of Rheumatology. 2009;36(11):2531-8.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.
30. Gabriel SE, Crowson CS, O'Fallon WM. A comparison of two comorbidity instruments in arthritis. Journal of Clinical Epidemiology. 1999;52(12):1137-42.
31. Kelly C, Hamilton J. What kills patients with rheumatoid arthritis? Rheumatology. 2007;46(2):183-4.
32. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology. 2009;48(10):1309-13.
33. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.
34. Warrington KJ, Kent PD, Frye RL, Lymp JF, Kopecky SL, Goronzy JJ, et al. Rheumatoid arthritis is an independent risk factor for multi-vessel coronary artery disease: a case control study. Arthritis Research & Therapy. 2005;7(5):R984-91.
35. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis and Rheumatism. 2005;52(2):402-11.
36. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in 4 decades? The Journal of Rheumatology. 1999;26(12):2529-33.
37. Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. Rheumatology. 2013;52(1):45-52.
38. Solomon A, Norton GR, Woodiwiss AJ, Dessein PH. Obesity and carotid atherosclerosis in African black and Caucasian women with established rheumatoid arthritis: a cross-sectional study. Arthritis Research & Therapy. 2012;14(2):R67.
39. Yang X, Chang Y, Wei W. Endothelial Dysfunction and Inflammation: Immunity in Rheumatoid Arthritis. Mediators of Inflammation. 2016;2016:6813016.

40. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. Rheumatology. 2001;40(6):640-4.
41. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology. 2008;47(1):72-5.
42. Fitzgerald GA. Coxibs and cardiovascular disease. The New England journal of Medicine. 2004;351(17):1709-11.
43. Marks JL, Edwards CJ. Protective effect of methotrexate in patients with rheumatoid arthritis and cardiovascular comorbidity. Therapeutic Advances in Musculoskeletal Disease. 2012;4(3):149-57.
44. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002;106(17):2184-7.
45. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis and Rheumatism. 2005;52(2):412-20.
46. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation. 2003;108(19):2317-22.
47. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis and Rheumatism. 1994;37(4):481-94.
48. Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, Vassallo R, et al. Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study. Arthritis Care & Research. 2013;65(8):1243-50.
49. Shen TC, Lin CL, Wei CC, Tu CY, Li YF. The risk of asthma in rheumatoid arthritis: a population-based cohort study. QJM : monthly journal of the Association of Physicians. 2014;107(6):435-42.
50. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Archives of Internal Medicine. 2008;168(2):159-66.
51. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology. 2009;48(9):1069-72.
52. Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. The European Respiratory Journal. 2002;19(4):756-64.
53. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Seminars in Arthritis and Rheumatism. 2014;43(5):613-26.
54. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis and Rheumatism. 2002;46(9):2287-93.
55. Abdool Karim SS, Churchyard GJ, Karim QA, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. Lancet (London, England). 2009;374(9693):921-33.
56. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology. 2013;52(1):53-61.
57. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America. 2000;97(16):9203-8.

58. Haraoui BC, M. Champsaur, K. Luijtens, E. Keystone. Effects of different steroid doses on adverse events and radiographic progression of certolizumab pegol-treated rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2014;01(71):498.
59. Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. Arthritis Research & Therapy. 2011;13(4):R139.
60. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L. Methotrexate, rheumatoid arthritis and infection risk: what is the evidence? Rheumatology. 2009;48(8):867-71.
61. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Research & Therapy. 2008;10(2):R45.
62. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(33):5216-22.
63. Fries JF, Murtagh KN, Bennett M, Zatarain E, Lingala B, Bruce B. The rise and decline of nonsteroidal antiinflammatory drug-associated gastropathy in rheumatoid arthritis. Arthritis and Rheumatism. 2004;50(8):2433-40.
64. Curtis JR, Xie F, Chen L, Spettell C, McMahan RM, Fernandes J, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. Arthritis and Rheumatism. 2011;63(2):346-51.
65. Hirohata S, Inoue T, Ito K. Development of rheumatoid arthritis after chronic hepatitis caused by hepatitis C virus infection. Internal Medicine (Tokyo, Japan). 1992;31(4):493-5.
66. Maillefert JF, Muller G, Falgarone G, Bour JB, Ratovohery D, Dougados M, et al. Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2002;61(7):635-7.
67. Clifford BD, Donahue D, Smith L, Cable E, Luttig B, Manns M, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology (Baltimore, Md). 1995;21(3):613-9.
68. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Annals of the Rheumatic Diseases. 2003;62(11):1078-82.
69. Haugeberg G. Focal and generalized bone loss in rheumatoid arthritis: separate or similar concepts? Nature clinical practice Rheumatology. 2008;4(8):402-3.
70. Gough A, Sambrook P, Devlin J, Huissoon A, Njeh C, Robbins S, et al. Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis. The Journal of Rheumatology. 1998;25(7):1282-9.
71. Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet (London, England). 1994;344(8914):23-7.
72. Lodder MC, Haugeberg G, Lems WF, Uhlig T, Orstavik RE, Kostense PJ, et al. Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: the Oslo-Truro-Amsterdam (OSTRA) collaborative study. Arthritis and Rheumatism. 2003;49(2):209-15.
73. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis and Rheumatism. 1992;35(5):498-502.
74. Sliwa K, Ojji D, Bachelier K, Böhm M, Damasceno A, Stewart S. Hypertension and hypertensive heart disease in African women. Clinical Research in Cardiology. 2014;103(7):515-23.
75. Sliwa K, Lyons JG, Carrington MJ, Lecour S, Marais AD, Raal FJ, et al. Different lipid profiles according to ethnicity in the Heart of Soweto study cohort of de novo presentations of heart disease. Cardiovascular journal of Africa. 2012;23(7):389-95.

76. Dessein PH, Woodiwiss AJ, Norton GR, Solomon A. Rheumatoid arthritis is associated with reduced adiposity but not with unfavorable major cardiovascular risk factor profiles and enhanced carotid atherosclerosis in black Africans from a developing population: a cross-sectional study. Arthritis Research & Therapy. 2013;15(4):R96.
77. Ogdie A, Maliha S, Shin D, Love TJ, Baker J, Jiang Y, et al. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology. 2017;56(6):907-11.
78. Seedat YK, Rayner BL. South African hypertension guideline 2011. South African Medical Journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2012;102(1 Pt 2):57-83.
79. Amod A, Ascott-Evans B, Berg G, Blom D, Brown S, Carrihill M, et al. The 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa Guideline for the management of type 2 diabetes (revised). Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2012;17(2):95.
80. Czerwinski E, Badurski JE, Marcinowska-Suchowierska E, Osieleniec J. Current understanding of osteoporosis according to the position of the World Health Organization (WHO) and International Osteoporosis Foundation. Ortopedia, traumatologia, rehabilitacja. 2007;9(4):337-56.
81. Kidney disease: Improving Global Outcomes clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International Supplement. 2009(113):S1-130.
82. National Clinical Guideline Centre. (2010) Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English.