

THE RISK FACTORS FOR PROGRESSION OF CHRONIC KIDNEY DISEASE IN A COHORT OF SOUTH AFRICAN BLACK PATIENTS

A thesis submitted in partial fulfilment
of the requirements for the degree of
Master of Medicine in Internal Medicine
At The University of the Witwatersrand

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0401790P

W-05-01-48

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August 2024

DECLARATION

I hereby declare that this research report submitted for the degree of Master of Medicine (MMed) in Internal Medicine, at the University of the Witwatersrand – Faculty of Health Sciences, is my own original work and has not been previously submitted to any other institution of higher education. I further declare that all sources cited in this document are acknowledged in the comprehensive list of references attached.

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ACKNOWLEDGEMENTS

First and foremost I would like to thank God who blessed me with the strength to complete this study.

I gratefully acknowledge the support and guidance of the Chris Hani Baragwanath senior medical staff, most particularly my MMed supervisors Dr Gloria Teckie, and Dr Nasrin Goolam Mahyooden. Without their supervision and thoughtful encouragement, this thesis would have never taken shape.

I am deeply grateful to the patients attending the Renal OPD clinic at Chris Hani Baragwanath Hospital who participated in this study.

I would also like to thank Mr Promise Khumbulo for assistance with the statistical analysis and language editing.

Most of all, my deepest thanks to Dr Midhya Naidoo, my wife for her understanding, wisdom, guidance and encouragement and for pushing me farther than I thought I could go.

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LIST OF ABBREVIATIONS AND NOMENCLATURE

ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
ARB	Angiotensin receptor blockers
ART	Anti-retroviral therapy
BP	Blood pressure
BMI	Body mass index
CKD	Chronic kidney disease
CHBAH	Chris Hani Baragwanath Academic Hospital
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMT1	Diabetes mellitus Type 1
DMT2	Diabetes mellitus Type 2
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
HDL/LDL	High- / Low density lipoprotein
HbA1c	Glycosylated haemoglobin
HIV	Human immunodeficiency virus
HIVAN	HIV associated nephropathy
HIV-ICK	HIV associated immune complex disease
KDOQI	Kidney Disease Outcomes Quality Initiative
RRT	Renal replacement therapy
SA	South Africa
UPCR	Urine protein : creatinine ratio
UA	Uric acid

1. LITERATURE REVIEW

Clinical Presentation of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function that have been present for over 3 months.^[1] It is a progressive condition that develops slowly in some individuals but rapidly in others and has adverse outcomes such as kidney failure, cardiovascular disease (CVD), and premature death.^[2] KDIGO describes CKD by indicators of renal damage, namely imaging or proteinuria (commonly using protein to creatinine ratio, PCR) and decreased renal function. CKD is commonly characterised as an eGFR of less than 60 mL/min/1.73 m² for over 3 months, which represents a significant loss of normal nephron functioning. The current recommendation is to use estimation equations such as the abbreviated Modification of Diet in Renal Disease (MDRD) equation, where creatinine is used in association with age, sex, and race to estimate glomerular filtration rate and CKD stage.^[1] The MDRD and Chronic Kidney Disease Epidemiology (CKD-EPI) equations have both shown satisfactory and comparable performance in a recent SA mixed-ancestry adult population, with the MDRD equation marginally less biased than the CKD-EPI.^[3]

The MDRD Equation: ^[1] $eGFR = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$

The categories of CKD as defined by eGFR include: ^[1]

1. CKD stage 1 eGFR > 90 mL/min/1.73 m² (with abnormal urine findings or imaging)
2. CKD stage 2 eGFR 60-89 mL/min/1.73 m²
3. CKD stage 3A eGFR 45-59 mL/min/1.73 m²
4. CKD stage 3B eGFR 30-44 mL/min/1.73 m²
5. CKD stage 4 eGFR 15-29 mL/min/1.73 m²
6. CKD stage 5 eGFR < 15 mL/min/1.73 m²

Recent guidelines have suggested that stage 3 be subdivided into 3a and 3b to reflect an increasing CVD risk with worsening kidney disease.^[4] A recent UK retrospective laboratory audit study estimated that most patients present with CKD stage 3 on presentation, with 84% of these stage 3a and 16% stage 3b.^[4] In developing countries, however, patients present late and are often postulated to have CKD if they present with a persistently elevated creatinine result or if they have a raised serum creatinine in addition to a low haemoglobin and echogenic kidneys on abdominal ultrasound.^[5]

Diseases that affect the kidney are often asymptomatic and detected with routine screening; however, they can also present with features of renal dysfunction or clinical signs related to an underlying systemic disease.^[6] Early CKD manifestations occur insidiously and often include symptoms such as malaise, loss of appetite, and sleep disturbances. The number and severity of symptoms usually increase with a worsening CKD stage.^[7] The more well recognised symptoms of nausea, vomiting, muscle cramps, and anasarca manifest at a later stage, when substantial time has been lost in trying to prevent the progression of the disease. This can be due to delayed referrals, low socioeconomic status, and the increasing role of alternative medical practitioners.^[8]

Prevalence of Chronic Kidney Disease

CKD has a worldwide distribution, and it has been estimated that approximately 500 million individuals globally are afflicted by the disease. However, studies suggest there is significant geographical and temporal variation in these patterns, with the prevalence increasing at a more rapid rate in developing countries.^[9] The magnitude of CKD in Sub-Saharan African countries is still poorly characterised, although there are speculations that the incidence rates are three times higher than those in developed countries.^[10] A systematic review of CKD done recently in sub-Saharan Africa described a prevalence of 13.9%. From this statistic, it can be estimated that CKD affects approximately 1 in 10 adults, and in black patients, the figure is possibly higher due to a low socioeconomic status and a high burden of obesity, hypertension, diabetes, and the human immunodeficiency virus (HIV).^[10] The two major causes of CKD worldwide are hypertension and diabetes mellitus (DM), and in developing countries, chronic glomerulonephritis and HIV are highlighted as additional key causes.^[11] This is likely due to an increased incidence of infections, a poorer response to therapy, and a higher rate of progression to end-stage renal disease (ESRD) within these populations. CKD is a significant cause of mortality whose global impact has continued to increase, making it the 18th highest cause of global deaths, up from a previous estimate of 27th.^[11] In South Africa (SA), CKD incidence has mirrored this change, doubling from 1990 to 2010 (138%).^[12] This degree of increasing incidence is observed to be second only to that of HIV and acquired immunodeficiency syndrome and can most likely be attributed to higher screening, as well as an increase in hypertension and glomerular diseases.^[12] In addition, in sub-Saharan Africa, CKD more commonly affects individuals aged between 20 and 50 years, and the average age of onset of ESRD is 20 years earlier in populations of African descent compared with other ethnic groups in Western countries (45 years vs. 63 years).^[13]

The 1994 South African Dialysis and Transplant Registry noted that glomerulonephritis (52.1%) and hypertension (45.6%) were the two highest contributors to ESRD.^[14] In all parts of Africa, research funding is significantly skewed in favour of infectious diseases. This contributes to inadequate data on CKD and decreased awareness among the general public, health providers, and the government.^[15] The increased attention currently being given to CKD worldwide is attributable to several factors: the rapid increase in its prevalence, the enormous cost of treatment and hospitalisation, an appreciation of the role it plays in increasing the risk of CVD, and the continued discovery of measures to slow its progression.^[15] However, despite a clear association with adverse outcomes, a recent review assessing the capacity for making effective CKD recommendations has identified gaps that limit research capacity globally, including inadequate funding and a low level of available infrastructure.^[16]

Factors that influence progression of Chronic Kidney Disease

Glomerular filtration rate generally declines with the ageing of the kidney at a rate of 1 mL/min/year in normal people.^[17] It was previously thought that CKD exhibited a predominantly linear progression pattern, with a more rapid decline of renal function at later stages. However, recent studies have shown that CKD progression may be highly heterogeneous, with patients exhibiting different trajectories of eGFR over time determined by individual patient factors and the initial CKD stage.^[18] The rate of eGFR decline can be a useful therapeutic target to monitor CKD progression, and a recent meta-analysis showed that a more rapid decline is clearly associated with an increased risk of ESRD, defined as kidney failure requiring dialysis or transplantation.^[19] A 10-year follow-up study in patients with initial CKD stage 3 showed a clear impact on outcomes for individuals based on the rate of eGFR decline, where patients with rapid progression (annual decline rate $>3 \text{ ml/min/1.73 m}^2$) reached ESRD within 5 years. Whereas individuals with a decline rate $<1 \text{ ml/min/1.73 m}^2$ tended to remain stable and not progress to ESRD during the 10-year follow-up period.^[20] Absolute annual eGFR decline rate can help clinicians to better predict the progression of CKD. Individuals with renal function decline rate over $3 \text{ ml/min/1.73 m}^2/\text{year}$ require closer monitoring and regular assessment for modifiable risk factors.^[20]

The number of patients with renal failure treated by dialysis and transplantation has grown dramatically in the United States, with the age-, sex-, and race-adjusted incidence of ESRD increasing by 43% during the decade following 1991.^[21] Patients who have ESRD and are older than 65 also doubled in this time period, with the fastest-growing group having an average age

greater than 75. It has been observed that minor reductions in the rate of decline in renal function early in the disease process can provide substantial benefits in delaying progression to ESRD.^[22] This suggests that an advantage can be gained from the early identification and treatment of risk factors in CKD patients. Improved understanding and regular monitoring to control key modifiable risk factors in patients are important for the prevention of CKD progression and for long-term clinical outcomes.^[23] Many low-income countries are not able to deal with these serious long-term consequences. Given the high costs of treating ESRD, it is unsurprising that the provision of renal replacement therapies is virtually non-existent in many parts of sub-Saharan Africa.^[24]

CKD is associated with several common adverse clinical complications, such as hypertension, bone mineral disease and acute kidney injury (AKI). The connection between AKI and CKD is becoming more well acknowledged, as it seems likely they promote one another.^[25] Numerous published meta-analyses have detailed how the severity of CKD, as defined by worsening eGFR and albuminuria, independently determines the risk of AKI.^[25] A growing body of literature also shows that AKI hastens the progression of CKD, with individuals who suffer dialysis-requiring AKI being at higher risk of experiencing worse long-term renal outcomes.^[26]

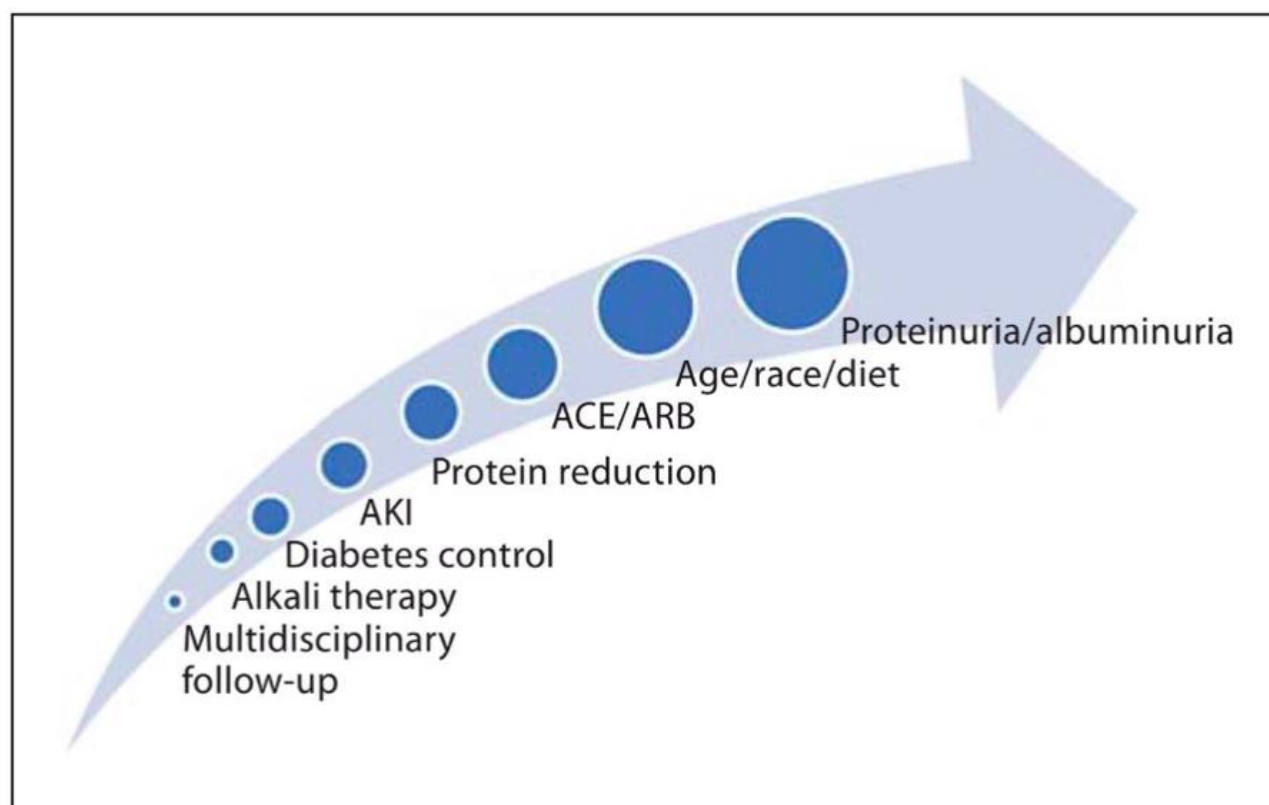


Figure 1 Clinical factors associated with trajectories of renal function. ^[27]

Underlying risk factors for chronic kidney disease

CKD is a complex and usually irreversible disease process with many aetiologies, where the cause, the presence of underlying risk factors, and the stage of the disease can dictate the rate of progression and loss of renal function. Risk factors can be classified into initiating factors that start the process of nephron loss, such as age and gender, and perpetuating factors that drive progression, such as hypertension and proteinuria.^[28] There are several primary non-modifiable risk factors involved in the progression of CKD, including age, gender, race, family history, and stage of CKD.^[29] Ageing is a natural physiological process that itself leads to a loss in the number of functional nephrons and ultimately to an average decline in the eGFR rate, estimated at approximately 6.3 ml/min/1.73 m² per decade. When age-related diseases are superimposed on this process of senescence, it can change the rate of functional decline and exhaust renal functional reserve.^[30] Two separate large meta-analyses showed a progressive decline in renal function with increasing age, with over 10% of adults older than 65 years suffering from CKD3a or worse.^[31] These meta-analyses also demonstrated that men exhibit a more rapid decline in eGFR with worse outcomes than women. This can most likely be attributed to gender-specific differences in glomerular structure, gene expression, and the activity of local hormones and cytokines.^[31] Multiple studies have shown that Africans are at increased risk for CKD occurrence and progression to ESRD.^[32] A significant increase in the condition-specific odds ratio associated with several forms of renal disease, including HIV-related nephropathy and focal segmental glomerulosclerosis, has been shown to be associated with individuals of African descent carrying the APOL1 genotype.^[33]

There are also a number of independent risk factors where optimal management, pharmacotherapeutic interventions, and lifestyle modifications improve both renal and cardiac outcomes.^[34] These modifiable risk factors include diabetes, hypertension, dyslipidaemia, elevated body mass index (BMI), proteinuria, smoking, and anaemia.^[35] The first four comprise a clustering of cardiovascular risk factors termed metabolic syndrome, which itself is regarded as an independent risk factor for CKD occurrence.^[36] The three most highly studied factors that are linked to influences on eGFR are hypertension, proteinuria, and the effects of therapies aimed at addressing these.^[37] Different types of outcomes are of interest in the course of CKD, such as the decline of eGFR and time-to-dialysis or transplantation. Previous single-centre studies have demonstrated that timely referral to a multidisciplinary CKD clinic programme for management produced the greatest increases in time to renal replacement therapy.^[38] Evidence has also shown that regular monitoring and prompt control of risk factors will improve

outcomes and retard disease progression.^[39] There are also predictors that may help us identify high-risk patients in the future, such as asymmetric dimethylarginine, fibroblast growth factor, and calcium phosphate metabolism.^[40] This would enable us to provide intensive medical surveillance and slow the progression to ESRD.

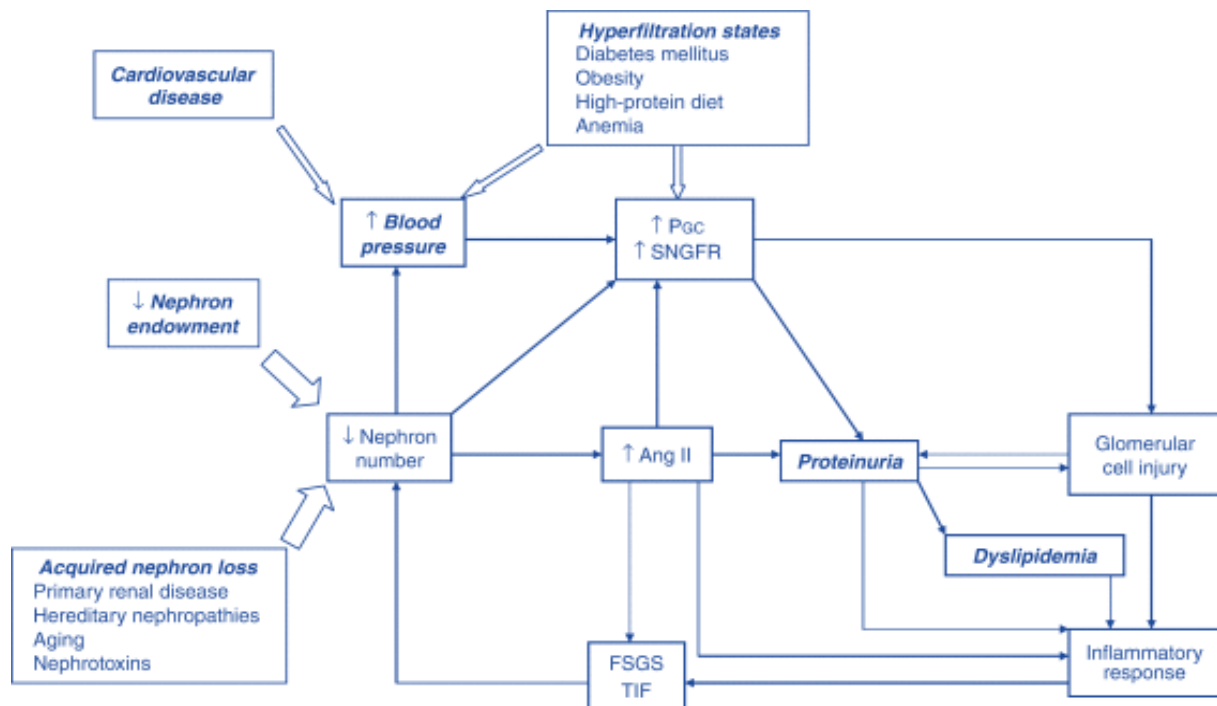


Figure 2 Interaction of risk factors for CKD progression with pathophysiological mechanisms that contribute to a vicious cycle of progressive nephron loss.^[41] *Ang II* – angiotensin II; *FSGS* – focal and segmental glomerulosclerosis; *Pgc* – glomerular capillary hydraulic pressure; *SNGFR* – single nephron glomerular filtration rate.

Diabetes

Diabetic nephropathy is a common complication of diabetes and is rapidly becoming the single most common cause of ESRD worldwide.^[15] The clinical course, traditionally seen in type 1 diabetic patients, is a first silent phase of glomerular hyperfiltration and is followed by mild albuminuria. After an average of 10–15 years post diagnosis, albuminuria progresses to overt proteinuria, and reduction in eGFR.^[42] However, research has observed that not all diabetic patients present with the classic phenotype, and some patients follow non-linear eGFR trajectories without albuminuria.^[43] The prevalence of severe albuminuria (higher than 30mg/mmol) in type 2 DM ranges from 5% to 48% depending on the studies, and in type 1 DM, from 8% to 22%.^[43] The earliest structural changes seen in diabetes are thickening of the basement membrane, mesangial matrix expansion, and loss of podocytes.^[44] The overall effect is high intraglomerular pressure and hyperfiltration. The changes seen in patients with Type 2 DM are similar to those with Type 1 DM, but they are more heterogeneous and less predictably

associated with clinical presentations.^[44] Multiple studies separating patients into ‘intensive’ and ‘conventional’ insulin therapy groups, show the benefit of strict glycaemic control on proteinuria, as well as a definite reduction in microvascular end-points.^[45] In these trials, an HbA1c of <6.5% is suggested to retard the onset and progression of diabetic microangiopathy. The updated KDOQI guidelines for diabetes and CKD recommend an HbA1c of approximately 7%.^[46] The intensive group in these studies demonstrated a marked reduction in progression.^[47] Thus, patient management needs to be individually optimised in order to attain control as well as reduce the risk of developing life-threatening hypoglycaemia and macrovascular complications at low target values.

Hypertension

Hypertension is both a cause and a consequence of CKD. This bidirectional relationship makes causal inference between these two traits difficult. There is substantial evidence to indicate that CKD is strongly linked to uncontrolled high BP and resistant hypertension, with an evident association between renal tubular atrophy and interstitial fibrosis, and the mean 24-hour ambulatory BP records.^[53] A meta-analysis of 84 randomised and non-randomised patient trials found that there was a substantial reduction in microvascular complications, and an overall improvement in rate of eGFR loss of 0.18 ml/min/1.73 m² per month for every 10mmHg drop in mean arterial pressure.^[54] The recommendation for CKD patients suggests a target BP of less than 135/80mmHg in most patients, and the SPRINT trial demonstrated a significant reduction in negative outcomes with intensive systolic BP control (<120) in high risk individuals, including patients with CKD and for those with >1 g/day of proteinuria.^[55] While there were benefits of tight blood pressure control, there were also concerns over a significant increase in orthostatic hypotension, electrolyte disturbance, and acute renal impairment.^[55]

Proteinuria

Proteinuria is common in both diabetic and non-diabetic patients with CKD, and is a strong risk factor for disease progression.^[46] In non-diabetic CKD, an 80% reduction in the relative risk of CKD progression per gram per day reduction in proteinuria has been shown.^[48] Independent of blood pressure (BP) control, studies have also demonstrated the impact of reduced proteinuria on the advancement of CKD. This is because proteinuria often signifies an ongoing inflammatory or haemodynamic process and albumin itself is thought to be toxic to the tubules.^[49] In the setting of HIV infection this may be secondary to comorbid kidney disease, treatment-related nephrotoxicity, or HIV-related glomerular diseases.

In a post hoc analysis of 273 patients with protein losing nephropathies, participants with the greatest short-term reductions in proteinuria also had the slowest losses in eGFR, regardless of BP control.^[50] Treatment with specific antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB); decreases mean arterial pressure, reduces proteinuria and slows CKD progression.^[51] In non-diabetic CKD, meta-analyses show that ACEI and ARB can reduce proteinuria. In diabetic CKD, meta-analyses demonstrate that ACEI in type 1 DM, and both ACEI and ARB in type 2 DM, decrease the probability of progression from micro- to macro-albuminuria, the progression to nephrotic syndrome and the rate at which renal dysfunction occurs.^[52]

Dyslipidaemia

CKD is commonly associated with lipid abnormalities, and recently several lipid profile variables have been linked with the onset and progression of kidney disease. Studies have revealed that in patients with CKD; elevated total cholesterol, apolipoprotein B levels and LDL-cholesterol, as well as lower HDL-cholesterol levels were all associated with more rapid decline in eGFR.^[56] Dyslipidaemia is a consequence of worsening renal disease and plays a part in the high cardiovascular morbidity and mortality seen in CKD patients, especially those with ESRD.^[57] Significantly, recent research has shown that lipids may cause direct damage to the tubulointerstitial and glomerular tissues, and altered lipoprotein cargo and particles may be the reason for the elevated CVD in patients with CKD.^[57] In addition to the synergistic nephroprotective effects of statins and renin-angiotensin system inhibitors, there is evidence that lipid-lowering therapies also mitigate renal injury in earlier stages of CKD.^[58]

Obesity

The prevalence of obesity has been shown in multiple studies to be increasing at a highly alarming rate, with many SA black patients over the age of 20 meeting the clinical criteria for metabolic syndrome.^[59] Central obesity has been directly linked to a two-fold increase in the development of CKD, with the Framingham Offspring Study demonstrating that an elevated BMI increased the odds of developing CKD by 23%.^[60] The effects of increased adiposity impact the kidneys directly via production of adiponectin, leptin and resistin.^[61] These increase inflammation and oxidative stress, and are implicated in the development of focal segmental glomerulosclerosis and glomerulomegaly, and increase the risk of progression to ESRD.^[62]

Hyperuricemia

Uric acid (UA) is an oxidative metabolite of purine in humans, and plays a significant role in the development and progression of CKD.^[63] Various factors can affect the serum UA, including drugs and daily dietary intake. Many large observational studies show a clear association between hyperuricemia and an increase in cardiovascular mortality, and some have reported an increased risk of adverse renal outcomes, including progression to ESRD in CKD patients.^[64] KNOW-CKD, a prospective cohort study, classified 2042 CKD patients into quartiles depending on their serum UA level. This study found the prevalence of advanced CKD was higher in patients with an increased UA level.^[65]

Anaemia

Chronic anaemia is a common complication of CKD, and tends to worsen with progressive renal disease. Anaemia in CKD is often related to the direct decrease in erythropoietin production in the failing kidney, but can also be secondary to various factors; such as effects of other chronic illnesses, to blood loss from haemodialysis and to nutrient deficiencies.^[66] Anaemia has been shown to contribute to disease progression through multiple ways such as, increased renal plasma flow, glomerular hyperfiltration, glomerulosclerosis and hypoxia of tubular cells with associated tubulo-interstitial damage.^[67] These mechanisms all contribute to worsening proteinuria, hypertension and ESRD. In the RENAAL study each 1 g/dl decrease in haemoglobin was associated with an 11% increase in the risk of ESRD, and multiple randomized studies have reported the renoprotective benefit associated with erythropoietin therapy.^[67]

Human Immunodeficiency Virus (HIV)

HIV is a common disease in SA and all HIV-infected patients have access to antiretroviral treatment irrespective of CD4 cell count.^[68] HIV positive patients are predisposed to an increased risk for retroviral related renal disease. The most common diagnoses obtained from biopsies of patients with HIV-CKD are glomerular-dominant nephropathies, namely HIV associated nephropathy (HIVAN), occurring typically in young African adults with advanced disease, and immune complex-mediated glomerular diseases.^[68] The spectrum of renal pathology in these individuals is diverse and can be categorised into lesions directly related to intrarenal HIV gene expression, lesions related to comorbidities, drug effects and immune dysregulation.^[69]

With the introduction of anti-retroviral therapy (ART), there has been a significant decline in the incidence of HIVAN.^[70] Multiple regional studies showed an improvement in renal function with ART irrespective of renal histology.^[70] Wearne et al. in South Africa reported that both HIVAN and HIV-ICD showed response to ART.^[71] Progression to ESRD has been reported to be more likely when the following parameters are present: significant proteinuria, severely reduced eGFR, hepatitis co-infection, diabetes mellitus and chronic interstitial fibrosis.^[72] The Development of Anti-Retroviral Therapy in Africa (DART) study also showed an improvement of eGFR by 1.9 – 6 mL/min/1.73 m² after 5 years of ART, and an improvement in median eGFR by 21% in Ugandan HIV CKD patients after being on ART for 2 years.^[73]

Smoking

Smoking is an important modifiable renal risk factor through mechanisms such as intrarenal vasoconstriction, and an increase in proinflammatory cytokines and oxidative stress. This ultimately leads to tubular dysfunction, tubular atrophy and glomerulosclerosis.^[74] All CKD patients should therefore be strongly encouraged to quit smoking and given psychological and pharmacological support to achieve this critical management goal. The association between cigarette smoking and CKD has been assessed in observational settings and a positive relationship between the two has been established. Smoking is therefore clearly associated with accelerated eGFR decline with current smokers having a lower eGFR at 5 years, as compared to ex-smokers and non-smokers.^[75]

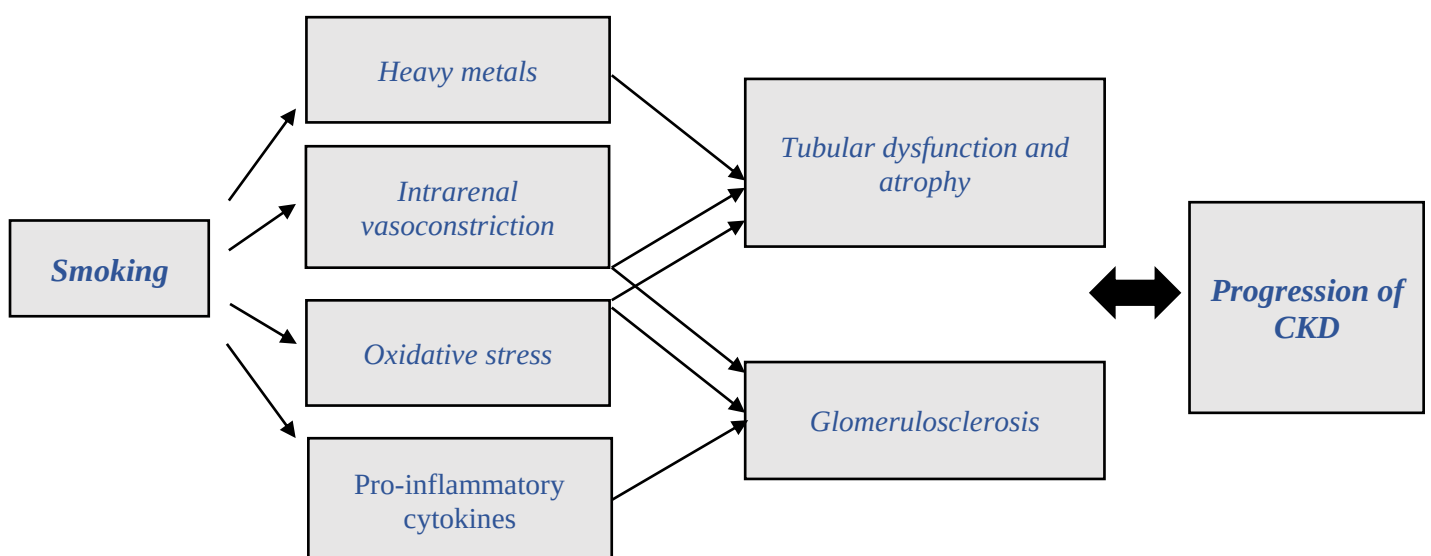


Figure 3 Overview of potential mechanisms for smoking induced renal damage.^[74]

Several causal mechanisms of CKD progression have been proposed through oxidative stress. This includes effects on mediator systems that are known to be involved in the genesis of progressive renal damage, cardiovascular compromise, increasing proteinuria and an overall detrimental effect on renal outcomes.^[76] Hunt II was a large trial with long term follow up and showed a significant influence of the cumulative smoking dose and a much lower risk after smoking cessation.^[76] In addition it has been shown that smoking cessation before renal transplantation resulted in better graft survival when compared to graft recipients who had continued smoking.^[77]

2. ABSTRACT

Background Increasing prevalence of chronic kidney disease (CKD) is a global health concern. Complex and heterogenous patient factors influence the natural course of CKD. We examined the relationship between predefined risk factors and the rate of progression and outcomes of CKD.

Methods Retrospective chart analysis was performed involving a cohort of 265 adult patients who presented at Chris Hani Baragwanath Hospital during 2010 to 2020. Descriptive statistics representing demographic profiles were examined, as well as associations between risk factors and outcomes. Estimated glomerular filtration rate (eGFR) decline was computed based on the recorded annual eGFR measurements. To examine the relationship between risk factors, eGFR change rate, and categorical patient outcomes, regression analysis was performed.

Results The mean age of participants was 56.6 (13.8) years; males constituted 144 (54%) of the study group. Major risk factors included hypertension (83%), diabetes (39%), and HIV (35%). Many patients were impacted by multiple concomitant risk factors (61%), with hypertension being a co-morbid diagnosis in >50% of patients with diabetes and HIV. The annual mean eGFR decline rate over four years was 1.63 mL/min/1.73 m². Decline rate was higher for diabetics: 2.3 mL/min/1.73 m² (SD 3.8), almost double that of non-diabetics. Baseline-stage CKD 3A progressed more rapidly than CKD 3B. The mean eGFR was 28.0 mL/min/1.73 m², with an average decline rate over the study period of 26%. Significant predictors of a higher than average rate of eGFR decline over the study duration were diabetes and dyslipidaemia (OR = 6.65 95% CI: 1.2–34.8). Age, HIV, and smoking also contributed to the rate of decline. Hypertension was not a strong prognosticator in the model. Acute kidney injury (AKI) was a frequent complication, noted in 44 (17%). When documented AKI cases with a significant decline in eGFR were excluded, the overall nature of the relationships reported based on the full sample remained unchanged.

Conclusions Common modifiable risk factors, when present at initial evaluation, were demonstrated to accelerate CKD progression and have worse outcomes. These patients are most likely to benefit from close monitoring, tighter risk factor control, and earlier planning for renal replacement therapy.

Key words chronic kidney disease, eGFR decline, diabetes, dyslipidaemia, age, smoking, HIV, hypertension

3. INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an abnormality in kidney function [e.g., estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or albuminuria ≥ 30 mg per 24 hours], persisting for at least 3 months, irrespective of the cause.^[1] CKD has a worldwide distribution, with an estimated global prevalence of 13.4%, and the prevalence is increasing at a more rapid rate in developing countries.^[2] The literature suggests that there is both a geographical and sociodemographic variation in CKD; however data from African countries is limited. A recent systematic review of CKD in sub-Saharan Africa reported a prevalence of 13.9%.^[3] In these countries, renal disease often leads to higher risks of requiring renal replacement therapy (RRT) and hospitalisation, likely secondary to delayed referrals, a poorer response to therapy, and a higher rate of progression to end-stage renal disease (ESRD).^[4]

CKD is a complex disease process where the aetiology, the presence of underlying risk factors, and the stage of the disease can dictate the rate of progression and loss of renal function.^[1,5] The two major causes of CKD worldwide are hypertension and diabetes mellitus; however, in developing countries, glomerulonephritis and HIV are highlighted as additional major causes.^[5] In South Africa, CKD incidence more than doubled from 1990 to 2010, with the degree of increasing frequency observed to be second only to that of HIV and mainly attributed to hypertension and glomerular diseases.^[6]

Glomerular filtration rate declines with age by roughly 1 mL/min/m² per year, beginning in the third decade of life.^[7] The rate of decline in eGFR is a useful therapeutic target to monitor CKD progression, and a recent meta-analysis showed that more rapid decline has a clear association with an increased risk of progression to ESRD and of mortality.^[7] A 10-year follow-up study in patients with initial CKD stage 3 showed a clear impact on outcomes for individuals based on the rate of decline, where patients with rapid progression (annual decline rate >3 mL/min/1.73 m²) reached ESRD within 5 years, whereas individuals with a decline rate <1 mL/min/1.73 m² tended to remain stable during the follow up period.^[8] The largest portion of CKD patients fit into the stage 3 category (eGFR 30-59 mL/min/1.73 m²), and only a small fraction of these patients will progress to ESRD. However, more rapid CKD progression often means worse clinical outcomes, independent of the current level of eGFR.^[9] Other studies using longitudinal eGFR measurements found rapid declines in kidney function to be independently associated with an increased risk for negative cardiovascular outcomes.^[10]

The average decline in renal function over time, in ml/min/1.73 m², recognises the ‘renal trajectory’ as an important element in patient management.^[11] It was previously believed that CKD displayed a predominantly linear progression pattern, with more rapid functional decline at later stages. However, recent studies allude to a large variation in CKD progression, where trajectories of eGFR over time fit non-linear patterns.^[11] Identifying the determinants of these new patterns and predicting who is at higher risk for CKD progression is relevant when prioritising resources, targeting patients who have the highest potential to intervene early and affect the natural course of the disease.^[12]

It has been observed that early identification and treatment of risk factors in CKD patients and a slower decline in eGFR early in the disease can provide substantial benefits in delaying CKD progression.^[13] Risk factors can be classified into initiating factors that start the process of nephron loss, such as age and gender, and perpetuating factors that drive progression, such as hypertension and proteinuria.^[14] The heterogeneity of risk factors influences the natural course of the disease. There are several primary non-modifiable risk factors involved in the progression of CKD, including age, gender, race, family history, and stage of CKD.^[15] There are also several independent risk factors where optimal management, pharmacotherapeutic interventions, and lifestyle modifications can be used to improve both renal and mortality outcomes.^[16] These modifiable risk factors include diabetes, hypertension, dyslipidaemia, elevated body mass index (BMI), proteinuria, smoking, and anaemia.^[17]

Chris Hani Baragwanath Academic Hospital (CHBAH) provides care to a majority low-income black population of over 3 million people from Soweto and the surrounding areas and is one of the primary specialist renal referral centres.^[18] Prior studies on CKD progression have been limited by underrepresentation of black patients and poorly reflect new therapies and management. These studies also focus on predictors of outcomes and do not consider serial renal function measurements.^[9] We conducted this retrospective study to determine the average rate of decline in renal function and to identify risk factors for disease progression at each stage of CKD. This will benefit us in risk stratification as well as providing information on the prognosis of individual patients.

4. METHODS

This study was a retrospective chart review of 265 black patients with CKD. A sample size of 265 patients was statistically significant to represent the approximately 5000 patients currently attending the Renal Clinic at CHBAH. This is achieved using a 95% confidence level and a 5% margin of error.^[19] Study used convenience sampling, where suitable cases were selected over a specific time frame. These patients were required to be registered in the outpatient clinic for a minimum follow-up of four years at any point between 2010 to 2020. Additional criteria to include patients consisted of a history, clinical diagnosis, and laboratory confirmation of CKD, as well as being stage 3-5 renal disease at presentation. For the purpose of this study, the assessment of race was based on the initial documented participant consultation, and collected solely from clinic medical records. Risk factors were identified on enrolment in the clinic. Ethics approval was obtained from the University of Witwatersrand Human Research Ethics Committee (ref no. M200303). Our objectives were to study the average rate of decline in eGFR in patients with CKD, to identify and describe the prevalence of non-modifiable and modifiable risk factors, and to establish their relationship to CKD outcomes in our cohort. We also considered the level of control of risk factors and the impact on the rate of eGFR decline in this patient population.

In order to facilitate comparison with data from related studies and to detect potential differences in CKD patterns over a significant duration, the 4-year period for which laboratory results were available was split into two 2-year intervals: time 0–2 years and time 2–4 years. This study used the Modification of Diet in Renal Disease (MDRD) equation to calculate eGFR from available serum creatinine measurements, which takes into account the patient's age, race, and gender.^[20] Data gathered included the demographic profile (age, gender, socioeconomic status), physical examination review, haematological and urine investigation results, and a record of renal disease outcomes. Data was collated onto an Excel spreadsheet and imported into IBM Statistical Package for Social Sciences (SPSS) version 28.0 for analysis. Descriptive statistics showed the demographic and clinical presentation profiles of patients in the study and were presented as frequencies and percentages for categorical variables. The data on the main continuous variables of age and eGFR did not deviate significantly from a normal distribution and were therefore reported as mean and standard deviation. Associations between the patient outcomes and the risk factors were examined using Pearson's chi-square and Fisher's exact tests for categorical variables and the independent samples t-test and one-way analysis of

variance (ANOVA) for continuous variables. The eGFR annual decline rate over the four years was computed based on the recorded eGFR annual scores. The relationship between the eGFR annual decline rate and the different patient demographics and risk factors was examined through multiple linear regression modelling. Statistical significance testing was set at the 95% confidence level, and therefore $p < 0.05$ indicated statistical significance.

Modelling with average rate of decline in eGFR

To examine significant risk factors for binary complications and outcomes in our patient cohort studies (i.e., AKI, CVD, ESRD, RRT, and death), logistic regression modelling was performed. AKI refers to documented cases with an abrupt decrease in kidney function, and cardiovascular disease (CVD) was described as a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, and peripheral arterial disease.^[21,40] The model was applied to the data to obtain odds ratios (OR) for comparing groups with different sets of characteristics.^[22] Our study modelled how the resultant decrease in eGFR was affected by independent variables, which included demographics, medical co-morbidities, and baseline creatinine.^[23] The coefficient estimated the change in log odds for each unit change in the dependent variable. The constant represents the log odds of the dependent variable.^[24]

Univariate analysis was used to compare the independent variables (demographics, medical co-morbidities, and baseline creatinine) and dependent variables to identify important covariates associated with the average decline in eGFR. One dependent variable was tested at a time. A chi-squared test was used if the independent variable was discrete or categorical. A paired-samples t-test was used if the independent variable was continuous. The independent variables were advanced towards the model, and other dependent variables were excluded. The advanced independent variables consisted of all variables of clinical importance with a p-value < 0.2 . Collinearity is the duplication of the predictive variable, which may influence the model too strongly and provide inaccurate results; if collinearity occurred, the variable with the lower p-value was advanced. The backward, stepwise, manual intelligent method of modelling was applied. Confounders were removed. The odds ratio of the dependent variable and co-efficient were checked. The main effects model, which contained the important variables, was built.

5. RESULTS

5.1 Overview of records reviewed

The medical charts of 265 patients who attended the CHBAH at various points between 01 Jan 2010 and Jan 2020 were reviewed. The main demographic characteristics as well as the respective frequencies and percentages of all categorical variables in the data set are summarised in Table 1. At baseline, the mean age of all patients was 56.6 ± 13.8 years. The youngest patient was 20 years old and the oldest patient 78 years. There was a higher number of males in the study sample at 54% (144 patients). All the patients included in the study were black, which reflects the majority of patients treated in the clinic. The major modifiable risk factors that were observed in our nephrology clinic were hypertension, diabetes mellitus, dyslipidaemia, obesity, smoking and HIV. Data from the study demonstrated prevalence rates of hypertension of 220 (83%) patients, diabetes mellitus 103 (39%) patients, and HIV 93 (35%) patients.

The overall number of patients with complications was 91 (34%), with the most common complications encountered being AKI 44 (17%) and CVD 30 (11%). Other outcomes included patients who had ESRD and required RRT, and death. There was a total of 18 patients (7%) who received RRT as an outcome of CKD during the study observation period. Due to limited access to dialysis services and loss of data, these cases were most likely underreported. Examples of missing data include patients who were lost to follow-up, transferred to dialysis programs, or incomplete medical records.

In the cohort, the association between each baseline characteristic and patient demographics such as age and gender was analysed using univariate analysis and is presented in Table 2 (for categorical variables). It was found that the modifiable risk factors hypertension, diabetes and HIV had a strong significance to age, and that smoking had a significant relationship to gender ($p = 0.00$).

Table 1 *Summary of patient characteristics and comorbidities*

	Mean (SD)	N=265, n (%)
DEMOGRAPHICS		
Age (years)	56.6 (13.8)	-
Duration in Clinic (years)	6.1 (2.4)	-
Gender		
• Male	-	172 (65)
• Female	-	63 (24)
Employed	-	55 (21)
Defaulted appointments	-	82 (31)
RISK FACTORS		
Hypertension	-	220 (83)
Dyslipidaemia	-	126 (48)
Diabetes Mellitus	-	103 (39)
HIV positive	-	93 (35)
Body Mass Index		
• Underweight	-	23 (9)
• Normal	-	101 (38)
• Overweight	-	75 (28)
• Obese Grade I	-	38 (14)
• Obese Grade II	-	20 (8)
• Obese Grade III	-	8 (3)
Smoking		
• Non-smoker	-	172 (65)
• Ex-smoker	-	63 (24)
• Smoker	-	30 (11)
MEDICAL THERAPY		
ACE-I	-	140 (53)
ARB	-	61 (23)
Compliance to treatment	-	211 (80)
COMPLICATIONS AND OUTCOMES		
Acute Kidney Injury	-	44 (17)
Cardiovascular Disease	-	30 (11)
RRT	-	18 (7)
Death (recorded in chart)	-	4 (2)

Table 2 Baseline univariate analysis showing clinical characteristics and patient demographics

GENDER	n (%)			p-value
	Non-smoker	Ex-smoker	Smoker	
Smoking				
Female (N=121)	95 (79%)	24 (20%)	2 (2%)	0.00
Male (N=144)	77 (53%)	39 (27%)	28 (19%)	
Hypertension				
		Yes	No	0.32
Female (N=121)		97 (80%)	24 (20%)	
Male (N=144)		123 (85%)	21 (15%)	
Diabetes Mellitus				
Female (N=121)		52 (43%)	69 (57%)	0.25
Male (N=144)		51 (35%)	93 (65%)	
Dyslipidaemia				
Female (N=121)		59 (49%)	62 (51%)	0.81
Male (N=144)		67 (47%)	77 (53%)	
HIV				
Female (N=121)		47 (39%)	74 (61%)	0.25
Male (N=144)		46 (32%)	98 (68%)	
Employed (N=55)		28 (51%)	27 (49%)	0.01
Unemployed (N=210)		65 (31%)	145 (69%)	

AGE	Mean age (SD)			p-value
	Non-smoker	Ex-smoker	Smoker	
Smoking	56.9 (14.2)	58.4 (13.6)	51.5 (10.7)	0.07
		Yes	No	
Hypertension		57.9 (13.8)	50.7 (12.3)	0.00
Diabetes Mellitus		61.0 (13.9)	53.9 (13.1)	0.00
Dyslipidaemia		58.1 (14.0)	55.3 (13.6)	0.10
HIV		50.8 (10.2)	59.8 (14.5)	0.00

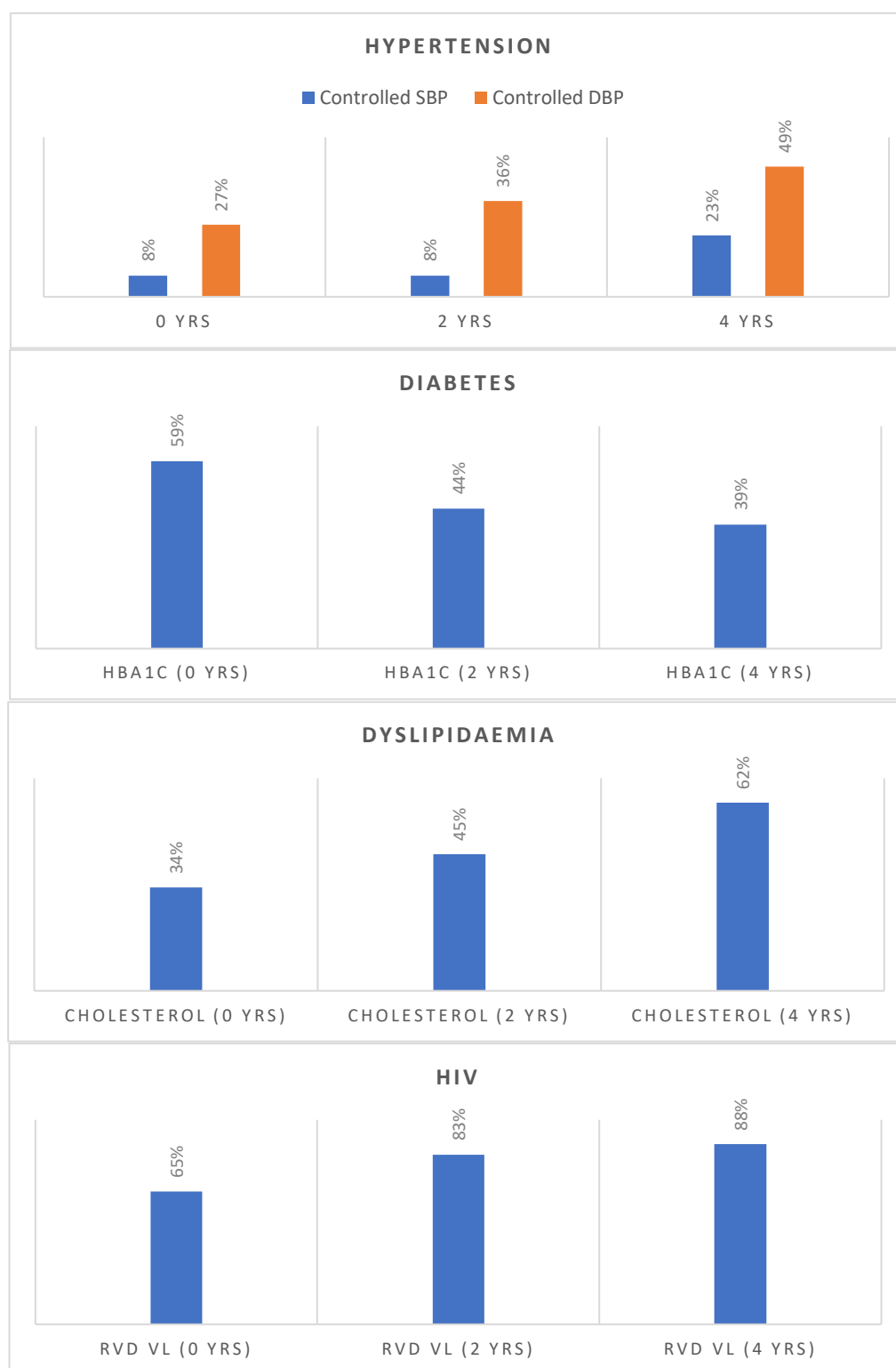
p<0.05 = statistically significant

The biochemistry breakdown at each time frame and mean annual values are outlined in Table 3 below.

Table 3 *Change in mean biochemical parameters over time*

	Mean (SD)				
	0 years	2 years	4 years	Change over 4 years.	Annual change rate
eGFR (mL/min/1.73 m ²)	34.6 (13.8)	32.0 (13.2)	28.1 (13.5)	6.6 (12.4)	-1.6 (4.1)
Creatinine (µmol/l)	223.9 (158.3)	215.8 (115.8)	273.9 (215.0)	49.5 (260.8)	12.4 (65.2)
SBP (mmHg)	146.8 (27.3)	146.7 (64.1)	133.9 (20.0)	-13.0 (32.7)	-3.3 (8.2)
DBP (mmHg)	90.0 (17.1)	90.1 (44.6)	83.7 (39.4)	-6.2 (79.3)	-1.6 (43.0)
HbA1c (%)	7.7 (3.5)	7.7 (2.3)	7.0 (2.1)	-0.7 (3.3)	-0.2 (0.8)
BMI (kg/m ²)	27.1 (6.2)	28.1 (6.6)	28.0 (6.1)	0.8 (4.2)	0.2 (1.0)
Cholesterol (mmol/l)	5.1 (1.4)	5.9 (3.4)	4.4 (0.7)	-0.8 (1.3)	-0.2 (0.3)
Haemoglobin (g/dl)	13.1 (2.1)	12.7 (7.0)	11.3 (2.0)	-1.8 (2.3)	-0.5 (0.6)
Urine Dipstix (g/l)	1.2 (0.7)	0.3 (0.7)	0.3 (1.0)	-0.9 (1.2)	-0.2 (0.3)
Urine PCR (mg/mg)	0.2 (0.4)	0.1 (0.5)	0.7 (5.4)	0.6 (6.3)	0.1 (1.6)
Albumin (g/l)	39.3 (27.6)	36.2 (11.7)	39.3 (6.9)	0.0 (27.6)	0.0 (6.9)
Uric acid (mmol/l)	0.3 (0.1)	0.3 (0.2)	0.3 (0.2)	0.0 (0.2)	0.0 (0.0)

Patients with hypertension, dyslipidaemia, diabetes, and HIV were documented. At each time interval, we looked at their level of control based on BP target 120/80 mmHg for hypertension (HPT), serum total cholesterol target <5.2 mmol/l, HbA1c <7% for diabetes mellitus (DM), and suppressed viral load for HIV. For the purpose of this study, we have used KDIGO and SEMDSA guidelines (Figure 4).^[1,28]



Abbreviations: SBP-Systolic blood pressure, DBP-Diastolic blood pressure, HbA1c-HaemoglobinA1c, HIV VL-Viral load (Suppressed)

Figure 4 Level of control of major risk factors for CKD progression in our cohort

5.2 The average rate of decline in eGFR

In our study cohort of patients with CKD stage 3-5, the mean eGFR after 4 years was 28 mL/min/1.73 m². As demonstrated in Table 4, there was an overall decline in eGFR in CKD clinic patients over the four years. The mean decline in eGFR over the first two-year period was 2.66 mL/min/1.73 m² and 3.86 mL/min/1.73 m² over the second two-year period. A paired sample t-test run shows that although the decline was greater in the second two-year period, this was not a statistically significant difference ($p = 0.29$) for the sample sizes available. The overall annual average decline rate over the four years was 1.63 mL/min/1.73 m² per year. Patients who started treatment in the renal clinic at baseline stage CKD 3A progressed more rapidly than CKD 3B, while those in stage 5 had an overall net improvement of 4.7 mL/min/1.73 m² (Figure 5).

There were no significant differences in the annual change in the eGFR between the different patient demographics (age, gender, socioeconomic status) and no statistically significant linear relationship between patient age and the eGFR annual decline rate ($R = -0.11$, $p = 0.08$). The results are graphed below in Figure 6. However, there were significant differences in the eGFR annual decline rate according to patient status in relation to HPT, DM, dyslipidaemia and HIV. The presence of these risk factors was associated with significantly higher eGFR annual decline rates, except for HIV, which was associated with a lower eGFR decline rate. The three risk factors found to be associated with higher eGFR annual decline rates were then included as covariates in a multiple linear regression model to determine the extent of their relative influence on eGFR decline. Both DM ($t = -1.87$, $p = 0.02$) and dyslipidaemia ($t = -2.10$, $p = 0.04$) were shown to be significant predictors of the eGFR decline rate in the cohort.

Table 4 Analysis of eGFR rate of decline over 4 years

eGFR annual mean scores	Mean (SD)	95% CI	p-value
0 years	34.6(13.8)	32.9 to 36.3	
2 years	32.0(13.2)	30.3 to 33.6	
4 years	28.1(13.5)	26.4 to 29.7	
Overall eGFR annual change rate	-1.6(4.1)	-2.1 to -1.1	

Comparison of mean eGFR annual changes

0-2yrs	-2.7(14.7)	-4.5 to -0.9	0.29
2-4yrs	-3.9(9.1)	-5.0 to -2.7	

eGFR annual decline rate by risk factors**Hypertension**

No	- 0.6(4.2)	-1.8 to 0.7	0.05
Yes	-1.9(4.0)	-2.4 to -1.3	

Dyslipidaemia

No	-1.0(4.2)	-1.7 to -0.3	0.01
Yes	-2.3(3.7)	-3.0 to -1.6	

Diabetes

No	-1.2(4.1)	-1.8 to -0.5	0.02
Yes	-2.3(3.8)	-3.1 to -1.6	

HIV

No	-2.1(4.1)	-2.7 to -1.4	0.02
Yes	-0.8(3.9)	-1.6 to 0.0	

Influence of risk factors on eGFR decline

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
HPT	-1.02	0.67	-0.10	-1.52	0.13
DM	-1.19	0.54	-0.11	-1.87	0.02
Dyslipidaemia	-1.05	0.50	-0.13	-2.10	0.04

p<0.05 = statistically significant, Unstandardised B coefficient = effect size

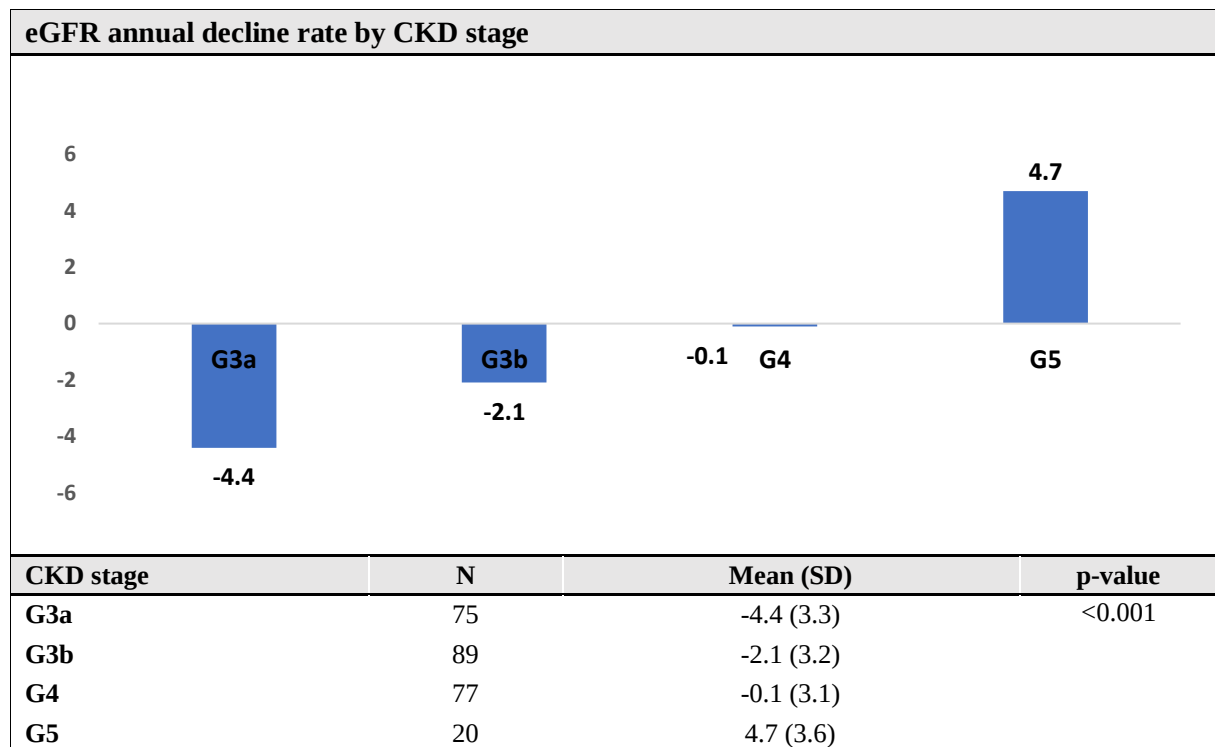


Figure 5 Correlation between eGFR annual decline rate by CKD stage

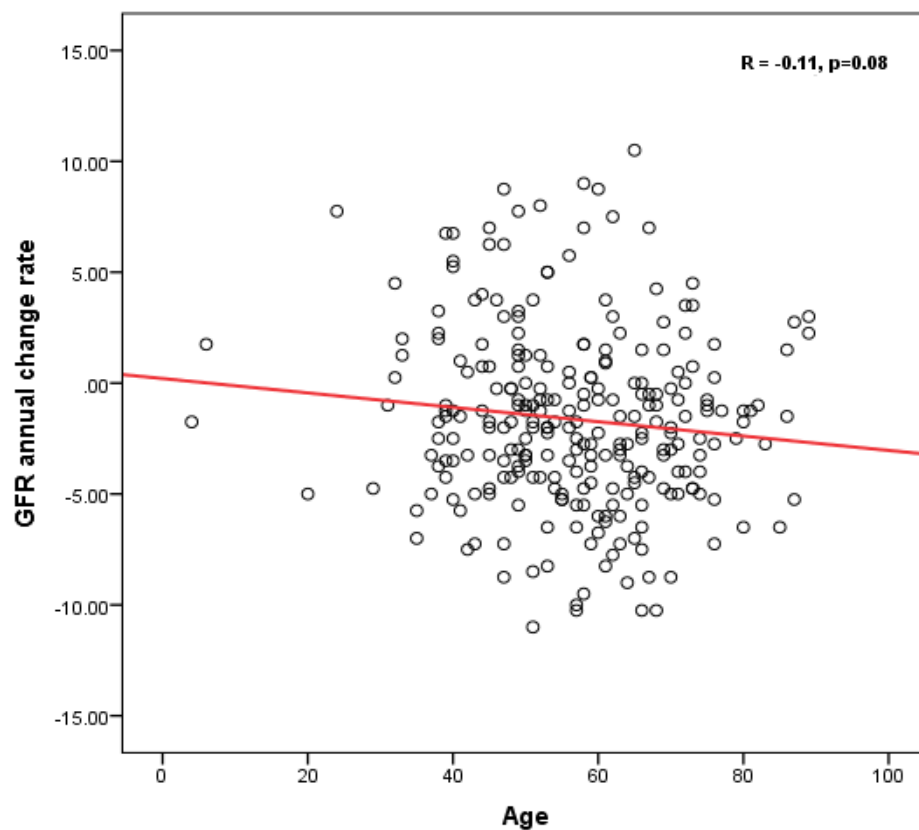


Figure 6 Correlation between eGFR annual decline rate and age

5.3 Logistic regression model for causes of eGFR decline

The regression analysis included an exploratory assessment achieved by using all the predictors in a univariate test against the outcome of average EGFR decline. Final model was fitted using the exploratory variables advanced after the univariate analysis. Hypertension was not a strong predictor in our model.

Diabetes and dyslipidaemia were found to significantly influence average eGFR decline in our cohort, with age, smoking, and HIV contributing to a lesser degree. Our study had 90 patients above the average (i.e., they progressed at a faster rate), which is the outcome of interest we were building our model to predict. The final model shows that the odds ratio of having a higher than average eGFR decline over 4 years is 6.65 (95% CI: 1.3-34.9, p-value 0.03). It is these patients who are likely to have the worst progression, falling into the lower third of subjects. (See supplementary material and data for further detail.)

Table 5 Associations for patients with increased risk of progression

Predictors	OR	95% CI	p-value
Age	1.1	1.00 – 1.3	0.46
HIV	1.1	0.3 – 1.3	0.09
Smoking	1.0	0.7 – 1.5	0.05
Diabetes	1.3	0.7 – 2.4	0.04
Dyslipidaemia	1.5	0.8 – 2.6	0.01
Combined risk	6.6	1.3 – 34.9	0.03

p<0.05 = statistically significant; OR = Unadjusted odds ratio

5.4 Complications and Outcomes

Table 6 Influence of risk factors on complications and outcomes

	n (%)	p-value	OR	95% CI	p-value
Total Complications					
Smoking					
Non-smoker (ref)	47(27)	0.01	2.3	1.3 – 4.2	0.01
Ex-smoker	29(46)				
Smoker	15(50)				
Dyslipidaemia					
No (ref)	34(27)	0.02	1.5	0.3 – 2.9	0.02
Yes	57(41)				
Renal Replacement Therapy					
Smoking					
Non-smoker (ref)	47(27)	0.01	2.3	1.3 – 4.2	0.01
Ex-smoker	29(46)				
Smoker	15(50)				
Dyslipidaemia					
No (ref)	14(10)	0.03	0.3	0.1 – 1.0	0.06
Yes	4(3)				
CKD stage					
G3a (ref)	1(1)	0.01	3.9	0.4 – 37.3	0.23
G3b	4(4)				
G4	8(10)				
G5	5(25)				
Death					
Smoking					
Non-smoker (ref)	47(27)	0.01	2.3	1.3 – 4.2	0.01
Ex-smoker	29(46)				
Smoker	15(50)				
Cardiovascular Disease					
Dyslipidaemia					
No (ref)	9(6)	0.01	2.4	1.0 – 5.7	0.04
Yes	21(17)				
Age (years)					
	Mean (SD)	0.01	1.1	1.0 – 1.1	0.01
CVD (No) (ref)	55.6(13.8)				
CVD (Yes)	64.7(11.5)				
BMI					
CVD (No) (ref)	27.2(5.9)	0.03	1.0	1.0 – 1.1	0.09
CVD (Yes)	30.0(8.0)				
Acute on Chronic Kidney Disease					
Dyslipidaemia					
No (ref)	34(24)	0.01	0.3	0.1 – 0.6	0.01
Yes	10(8)				

p<0.05 = statistically significant;

Table 7 *Baseline univariate analysis for complications and outcomes*

GENDER	Complications		RRT		Death		Cardiovascular Disease		AKI	
	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value
Male (N=144)	51(35)	0.70	12(8)	0.33	2(1)	1.00	16(11)	1.00	22(15)	0.62
Female (N=121)	40(33)		6(5)		2(2)		14(12)		22(18)	

AGE	Complications		RRT		Death		Cardiovascular Disease		AKI	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
No	56.5(13.7)	0.77	56.8(14.1)	0.38	56.8(13.8)	0.07	55.6(13.8)	<0.001	57.3(13.5)	0.10
Yes	57.0(14.1)		53.9(8.8)		44.3(13.0)		64.7(11.5)		53.5(15.0)	

p<0.05 = statistically significant

Table 6 summarises the influence of risk factors on complications and outcomes. Total complications included hypertensive crises, infections, AKI, and CVD. Smoking and dyslipidaemia were the only risk factors associated with total complications. Smoking was significantly associated with complications ($p = 0.01$), with the prevalence being much higher among smokers (50%) when compared to that of non-smokers (27%). Chances of developing complications were doubled among ex-smokers ($OR = 2.3$, 95% CI: 1.3-4.2) and almost three times higher among current smokers ($OR = 2.6$, 95% CI: 1.2-5.9). Smoking was also the only risk factor that could be correlated with death for the current sample size available. As expected, CKD stage 4 and 5 patients were reported as having a 10 times and 27 times higher chance of undergoing RRT, respectively.

Patients with CVD included those with coronary artery disease, stroke, and peripheral arterial disease. As highlighted in Table 7, these patients were significantly older (mean age 64.7 ± 11.5 years) compared to those without CVD (55.6 ± 13.8 years). The risk factor most highly associated with cardiovascular outcomes was elevated total cholesterol, with 21 of 30 patients receiving treatment for dyslipidaemia prior to adverse outcomes. Results for BMI can be narrated as an odds ratio of 1.0, indicating that the odds of an adverse outcome are similar to the odds of exposure among controls. In our cohort, a unit increase in age increased the odds for CVD by 10%, and a unit increase in cholesterol increased the odds for CVD by over 100%.

In our analysis, there were 44 patients who experienced a documented case of AKI that significantly dropped their eGFR, either on presentation or at any time during the study period. The average percentage rate of eGFR decline in all patients was approximately 26%. However, post-acute phase, with or without temporary dialysis, it improved by 13% for patients who had an AKI, indicating a net recovery and improvement in the baseline eGFR (Figure 7). Table 8 is based on the 221 cases after removing the AKI patients to review if excluding this group would change the results relating to the eGFR decline reported in the preceding sections. Altogether, although there are some changes in the value of the statistics, removing these cases does not change the overall nature of the relationships reported based on the full sample.

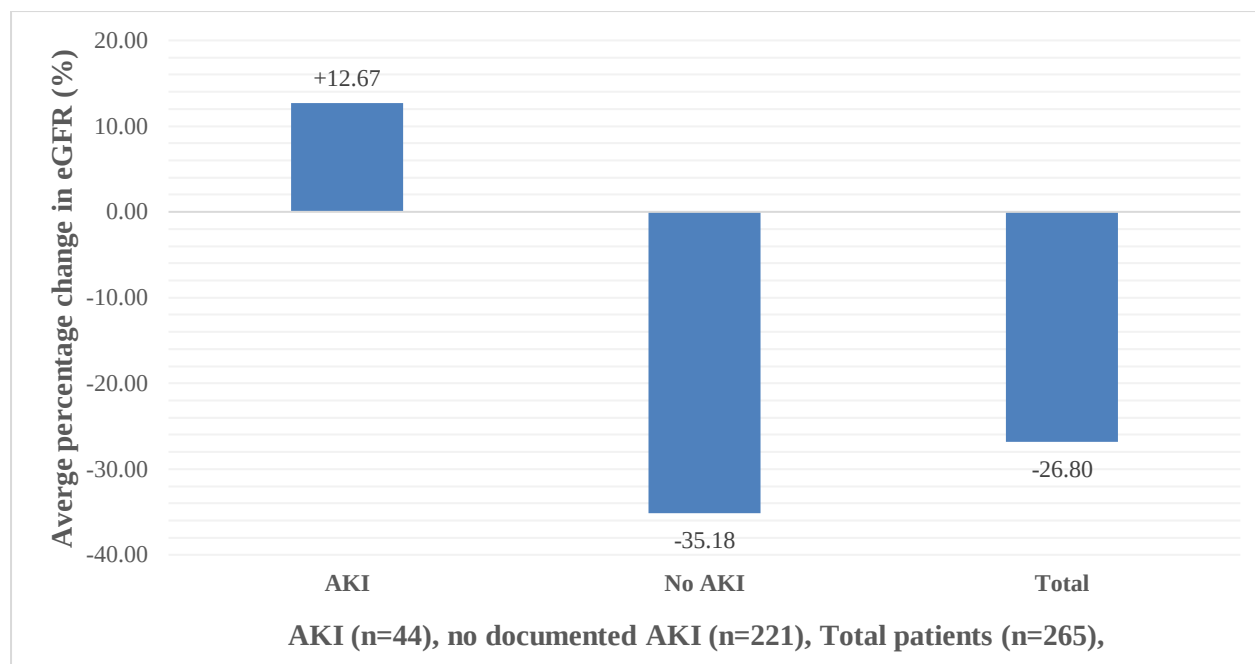


Figure 7 Average rate of eGFR change (%): acute kidney injury (AKI) vs no AKI

Table 8 eGFR Progression in patients without documented episode of AKI

	Mean (SD)	95% CI	p-value
0 years	35.0(14.2)	33.1 to 36.9	
2 years	32.5(13.1)	30.7 to 34.2	
4 years	27.1(18.3)	27.1 to 30.6	
Overall eGFR annual change rate	-1.5(4.2)	-2.1 to -0.95	
eGFR annual decline rate by CKD stage			
G3a	-4.3(3.4)	-5.1 to -3.5	<0.001
G3b	-2.1(3.3)	-2.9 to -1.3	
G4	0.2(2.8)	-0.5 to 1.0	
G5	5.4(3.2)	3.8 to 7.0	

p<0.05 = statistically significant

6. DISCUSSION

6.1 *The average rate of decline in eGFR*

Studies that calculate the decline in eGFR based on less than two serum creatinine determinations cannot definitively represent the progression of CKD. We therefore excluded patients with fewer than three MDRD determinations. The overall annual average decline in eGFR over the four years was estimated at 1.63 mL/min/1.73 m² per year, and the mean baseline eGFR was approximately 34 mL/min/1.73 m². The associations between baseline eGFR and the rate of eGFR decline are inconsistent between studies. In the MDRD study, the mean rate of GFR decline was not significantly related to baseline GFR.^[25] A post hoc analysis of the JUPITER study, however, revealed a strong correlation between the baseline eGFR and the degree of the eGFR decline, with greater reductions among subjects with eGFR > 60 mL/min/1.73m².^[26] This observation was supported by our results showing that patients presenting with an initial higher baseline eGFR were associated with a higher annual decline rate. REVEAL-CKD also showed that in advanced stages of CKD, equal changes in serum creatinine result in smaller changes in eGFR as well as an attenuation in annual eGFR decline following a diagnosis of CKD (3.20 mL/min/1.73 m² before diagnosis to 0.74 mL/min/1.73 m² after diagnosis).^[27] The CKD patients attending CHBAH Renal Clinic adhere to protective directions such as control of comorbidities, avoidance of NSAIDs and contrast, loss of weight, and smoking cessation. These recommendations would also slow the progression of eGFR decline over time. Our study also found that stage 5 patients gained 4.7 mL/min/1.73 m² during a four-year period. This group would most likely have the highest number of patients who died or were lost to follow up. Additionally, they may also have presented with an acute component (e.g. AKI), which they were treated for, resulting in a misinterpretation of their CKD stage and subsequent progression. Previous studies suggest an eGFR annual decline rate in CKD patients of more than 1 mL/min/1.73 m² is indicative of disease progression, whereas an annual decline rate less than 1 mL/min/1.73 m² is assumed to be the result of the normal ageing process.^[28] In the Baltimore Longitudinal Study on Aging, patients with normal renal function experienced an average decline in creatinine clearance of 0.75 mL/min per year in adults.^[28] Using our data, we found no statistically significant linear relationship between patient age and eGFR annual decline rate ($R = -0.11$, $p = 0.08$). The average rate of decline for all 265 patients was approximately 26%, suggesting the eGFR of a patient entering the clinic will be reduced on average by 26% four years later. This decline, which takes place over a longer interval, is less

likely to be due to a transient change or measurement error. According to a large meta-analysis, there was a substantial correlation between a reduction in eGFR measured as a percent change and the risk of ESRD and mortality.^[7] Nojima et al. measured the 1-year and 2-year eGFR decline intervals and reported the findings as an average percentage decline from a baseline measurement of 77.1 mL/min/1.73 m². They demonstrated that there was an 8.4% eGFR decline during a 1-year period and a 15.8% eGFR decline during a 2-year period from the baseline value. The study was performed with diagnosed type 2 diabetic patients and excluded subjects with AKI.^[29]

6.2 Independent risk factors

Multiple concomitant CKD risk factors were common (61%), with many patients having several co-morbidities. Hypertension was a co-morbid diagnosis in >50% of patients with diabetes and HIV. In all of the above groups, the control improved over the 4 years of study, except for the diabetic patients, in whom the percentage of patients adequately treated decreased from 59% to 33%. Multiple observational studies have shown diabetic treatment patterns in CKD patients differ from the general diabetic population and are highly variable, with a remarkably high proportion (>50%) receiving insulin-based therapies. Worse metabolic control with insulin monotherapy use has previously been observed in other patient populations, with an increased probability of HbA1C levels >7%.^[30] In advanced CKD, achieving adequate blood glucose levels can be difficult due to impaired renal clearance of insulin and an increased risk of hypoglycaemia, as well as inaccurate HbA1c measurements due to concomitant anaemia.^[31]

The data also looked to compare the presence of independent risk factors to the overall decline in eGFR. The presence of metabolic risk factors such as hypertension, diabetes mellitus, and dyslipidaemia was associated with significantly higher eGFR annual decline rates (-1.9; -2.3, $p<0.05$). While the HIV-positive patients, many of whom were virally suppressed on treatment, could be associated with a lower eGFR decline rate. Multiple clinical trials and laboratory studies prove the importance of viral load in the progression of HIV-related renal disease.^[32,33] Direct infection of podocytes and tubular cells has been linked with the development of HIV-associated nephropathy in human kidney biopsies; thus, it follows that treatment of active viral replication may retard the progression of renal dysfunction.^[33] Renal benefits of antiretroviral therapy were also noted in the DART and SMART trials.^[33] Furthermore, a multiple linear

regression model to determine the relative extent of their influence on eGFR decline ultimately proved both diabetes mellitus and dyslipidaemia to be important predictors of the eGFR decline rate in the clinic population group. Hypertensive patients and non-hypertensive patients experienced a small decline in eGFR, which was relatively close. These results depict the fact that individual patients may have more than a single risk factor, and therefore, independently assessing the risk factors is not a true representation of the eGFR decline, as well as indicating that risk factors not being assessed may be present and influence the outcome. According to a time-to-event outcomes meta-analysis of 304 publications investigating the quantitative outcome variables to track kidney function across time, the most often examined events in survival analyses were all-cause mortality, initiation of RRT, and decline of eGFR. A linear regression model was employed when a quantitative reduction in kidney function over time was the desired outcome. When the outcome of interest was binary, such as below or above an average percentage rate of decline in our study, the preferred model used was logistic regression.^[34] We thus proceeded to model our patients' eGFR decline with logistic regression to concurrently identify and measure the influence of factors related to a significant decline.

6.3 Regression model for causes of decline in eGFR

The regression model was fitted using the exploratory variables advanced after the univariate analysis. Baseline eGFR did not feature in the final model that depicted decline because of the net recovery experienced by the AKI patients. Our final model was reported in odds ratio (OR), showing that the OR of having a worse than average eGFR decline rate over 4 years is 6.65. Significant predictors of eGFR decline were diabetes and dyslipidaemia, with age, retroviral disease, and smoking also playing a role. It was these patients who were likely to have the worst outcome, falling into the lower third of patients. Hypertension was not a strong predictor in our model. This is likely due to the bidirectional relationship between hypertension and CKD, which makes causal inference between these two traits difficult.

Diabetes: In our study, most diabetic patients were significantly older, with a mean age of 61, and documented as having established diabetes mellitus type 2 (T2DM). The mean HbA1c was 7.46%, which was not a significant predictor of the presence of CKD progression (p value = 0.51). Many diabetic patients were diagnosed with new comorbid diseases and negative outcomes within the review period. The mean eGFR annual decline rate for diabetics was -2.3 ml/min/1.73 m² (SD 3.8), almost double that of non-diabetics. When included as a

covariate in our regression model to determine the extent of influence on eGFR decline in the cohort, diabetes was confirmed to be a significant predictor. In our assessment of risk factors that might explain the variation in decline seen among those with diabetes, we observed that $\text{SBP} \geq 140 \text{ mmHg}$, $\text{HbA}_{1c} \geq 10\%$, and insulin use were noteworthy. Zoppini et al. examined the predictors of eGFR decline in T2DM patients, who were monitored for a 10-year follow-up period to assess eGFR decline. They found that the annual decline in patients with T2DM and preserved kidney function was predicted by multiple modifiable risk factors, such as the presence of albuminuria and hypertension.^[35] In other recent studies, multidisciplinary management, including BP control with an ACEI as well as glycaemic and lipid control for T2DM, significantly decreased the progression of albuminuria and negative outcomes like ESRD.^[30,35] These studies quantified the impact of albuminuria on the development of eGFR trajectories following CKD stage 3 and demonstrated that diabetics with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ experience a progressive decline regardless of the albuminuria.^[36] In our model, we were unable to examine albuminuria accurately due to missing data in clinic files.

Dyslipidaemia: Our model ultimately showed dyslipidaemia to be a significant predictor of eGFR decline and negative outcomes, namely CVD ($\text{OR} = 2.4$, 95% CI 1.0–5.7), within the study cohort. The dyslipidaemia of CKD comprises primarily high total cholesterol (TC) and triglyceride (TG) levels and low levels of high-density lipoprotein (HDL). However, recent research indicates that CKD modifies the composition of lipoprotein particles, and these changes may be the root cause of the elevated CVD seen in CKD.^[37] The mean total cholesterol value decreased to 4.1 mmol/l over the review period with a negative annual change rate, representing an improved level of control. Statin usage has been demonstrated to be effective in lowering cholesterol in CKD and reducing CVD events in those with pre-end-stage CKD, but not in dialysis patients.^[37] As CKD progresses, dyslipidaemia often worsens, contributing to a higher prevalence of CVD and mortality. While the causal role between dyslipidaemia and the occurrence and progression of CKD appears to be clear, many studies have produced variable results in the relationship between lipid profiles and kidney function. Liang et al. analysed clinical data from 5183 participants to determine the odds ratio for incident CKD in regards to lipid profile. It was found that high levels of TC and LDL indicate a 1–2 times higher risk of CKD progression and renal dysfunction. This can be attributed to lipid-induced mitochondrial damage, macrophage infiltration, and foam cell formation within the kidney.^[38] Higher blood lipid levels were also independently associated with a greater likelihood of eGFR decline in the general population, as well as accelerating the development of ESRD.^[39]

6.4 Complications and outcomes

Cardiovascular Disease: CVD patients in our study were significantly older (64.7 ± 11.5) and showed a significantly increased mean BMI ($30.0 \text{ kg/m}^2 \pm 8.0$). The risk factor most highly associated with cardiovascular outcomes was high total cholesterol (OR=2.4, 95% CI 1.0–5.7). CKD, defined as either the onset of proteinuria or eGFR reduction, is found to predict higher CVD risk and is associated with an increase in all-cause mortality.^[40] This is partially explained by the fact that CKD is associated with an increased prevalence of traditional CVS risk factors. However, novel risk factors, such as inflammation, oxidative stress, and bone mineral disorders, are also highly associated with elevated CVS risk in patients with renal disease.^[39] The hypothesised mechanisms of damage due to declining renal function are to accelerate atherosclerosis and promote endothelial dysfunction, as well as the detrimental effects of chronic hypertension.^[41]

Acute kidney injury: Our study included 44 (17%) patients who were documented to have had a single episode of AKI in the four-year period. However, all episodes may not have been documented, and the consequences of other undocumented AKI cannot be excluded. Most of these cases were due to adverse effects secondary to medical therapy and other nephrotoxins, as well as dehydration, sepsis, and gout. Underlying CKD is now recognized as a clear risk factor for AKI, as studies show that both conditions are closely linked and have a bidirectional relationship.^[42] The prevalence of CKD and AKI increases with age, with the incidence of severe AKI being more than fifty times higher in people aged over 80 years when compared to people aged under 45 years.^[43] A 2008 study comparing 1,746 hospitalised adults who developed dialysis-requiring AKI with 600,000 hospitalised patients who did not showed significantly higher adjusted odds ratios for those with baseline eGFR 45–59 ml/min/1.73 m² when compared to CKD patients stage 1-2 and odds ratios up to 40.1 (95% CI 33.8–47.6) for those with baseline eGFR <15 ml/min/1.73 m².^[43] Subsequently, a growing body of research has connected AKI to the onset and progression of CKD. An excellent summary of the early literature can be found in a meta-analysis by Coca et al.^[44] Overall, patients who experienced documented AKI had an adjusted risk of CKD that was approximately nine times higher and an adjusted risk of ESRD progression that was three times higher. Furthermore, there was a grading of the association between AKI and CKD or ESRD, where a higher risk was linked to a greater severity of AKI.^[44]

REVEAL-CKD, a retrospective study of stage 3 CKD patients, found that delayed diagnosis and intervention were directly related to an increased risk of CKD progression (OR 1.40, CI 1.31–1.49). These findings included a higher risk of adverse cardiorenal outcomes, including myocardial infarction, stroke, hospitalisation for heart failure, and kidney failure.^[26]

7. STUDY LIMITATIONS

The retrospective nature of this chart review leads to several potential limitations. It is possible that some related data may not be included in the study due to inconsistent reporting and missing results in the recording and reporting of renal files during the course of the 10-year period. Nonetheless, every attempt was made to source records regarding pertinent outcomes, especially in cases of death. Deaths occurring before the minimum follow-up period would be excluded from analysis, which may result in an underestimation of mortality rates, as well as rate of progression.

The gold standard for measuring renal function is using plasma or urinary clearance of an exogenous filtration marker. Estimation of eGFR in our study was done using a creatinine-based formula. The precision of eGFR may be affected by numerous factors, and this can influence the estimation of CKD progression observed in this study.

The sample size selected is statistically representative of the population, however since non-probability sampling was utilised, it remains susceptible to sample bias and the inability to generalise.

8. CONCLUSION

This study contributes to our understanding of the complex interrelationship between risk factors and the progression of CKD over time, as well as the demographic variation of these comorbidities within our population. The review sample included a substantial HIV-positive cohort and covered a longer period than other studies from the region.

The overall annual average decline rate was 1.63 mL/min/1.73 m² per year, with an average rate of decline over the study period of 26%. Therefore, the eGFR of a patient entering the clinic will be reduced by roughly 26% four years later. The cohort was separated into those higher than the average, who declined at an increased rate, and those below the average, who performed better. Associations between patient risk factors and outcomes were also examined. Our final regression model to determine the clinic patients likely to have the worst outcome with more severe CKD progression showed that significant predictors of eGFR decline are diabetes and dyslipidaemia, with age, HIV, and smoking also contributing (OR = 6.65). To improve outcomes, it is recommended that these patients be counselled on their increased risk and the need to attend regular clinic follows-ups for close monitoring. Treating physicians should encourage more intensive control of risk factors and comorbid conditions. If circumstances allow, patients expected to decline at a faster rate should be earlier candidates for transplantation or dialysis work up.

Further prospective research regarding the progression of renal disease and studies linking outcomes in this area are recommended.

9. APPENDICES

Appendix 1: MMed Protocol submission



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PART-TIME OR FULL-TIME: FULL TIME			
FIRST REGISTERED FOR THIS DEGREE:	TERM: MARCH	YEAR: 2017	
DEPARTMENT: INTERNAL MEDICINE			
TITLE OF PROPOSED RESEARCH: TO INVESTIGATE THE RISK FACTORS FOR PROGRESSION OF CHRONIC KIDNEY DISEASE IN THE SOUTH AFRICAN BLACK POPULATION			
CANDIDATE'S SIGNATURE:			DATE: 10/08/2019
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SYNOPSIS OF RESEARCH: (Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s) [Use reverse side of this page if more space is required] INTRODUCTION AND AIM: Chronic Kidney Disease (CKD) has numerous complex causes and has a direct relationship with many illnesses. It has an ever-increasing impact on morbidity and mortality. The purpose of this study will be to understand the relationship between non-modifiable and modifiable risk factors, and the progression and outcomes of CKD in Black South African patients attending the Chris Hani Baragwanath Hospital Renal Outpatients Department.			

I. BACKGROUND LITERATURE ANALYSIS AND CRITIQUE

Prevalence and progression of chronic kidney disease

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for over 3 months. The current recommendation is to use estimation equations, where creatinine is used in association with age, sex, and race to estimate GFR and CKD stage, [Levey, 2002 KDOQI]. CKD is a progressive condition that develops slowly in some individuals, but rapidly in others, [Levey, 2007]. CKD is a significant cause of mortality whose global impact has continued to increase, making it the eighteenth highest cause of global deaths, from a previous estimate of twenty-seventh most common cause. This degree of increasing frequency is observed to be second only to that of HIV and AIDS, [Jha, 2013].

In developing countries chronic glomerulonephritis and interstitial nephritis are highlighted as additional significant causes of CKD, in part due to an increased incidence of bacterial and viral infections in these populations. A recent systematic review of CKD in sub-Saharan Africa reported a prevalence of 13.9%, [Stanifer, 2014]. In addition to the underlying aetiology of renal disease, the rate of CKD progression is dictated by the presence of risk factors, and how well these are controlled, [NICE, 2014]. The current management of patients is based on a number of clinical guidelines, which cover the identification of CKD, referral criteria to tertiary services and guidance on the management of complications, with little focus on encouraging practitioners to identify, assess and manage the risk factors which contribute to disease progression, [Nelson, 2012. KDOQI].

Rate of eGFR decline can be a useful therapeutic target to monitor CKD progression, and a recent meta- analysis showed that more rapid decline has a clear association with an increased risk of end stage renal disease (ESRD) and mortality, [Coresh, 2014]. A 10 year follow up study in patients with initial CKD stage 3 showed a clear impact on outcomes for individuals based on the rate of GFR decline, where patients with rapid progression (annual decline rate > 3 mL/min/1.73m²) reached ESRD within 5 years, whereas individuals with a decline rate <1 mL/min/1.73m², tended to remain stable and not progress to ESRD during the 10 year follow up period, [Tsai, 2017].

It has been observed that minor reductions in the decline in renal function early in the disease process can provide substantial benefits in delaying progression to ESRD, **[Düsing, 2006]**. This suggests that an advantage can be gained from the early identification and treatment of risk factors in CKD patients. Improved understanding and regular monitoring to control key modifiable risk factors in South African public health patients, is important for the prevention of CKD progression and for long-term clinical outcomes **[Gray, 2018]**. It has a worldwide distribution, and has adverse outcomes of kidney failure, cardiovascular disease, and premature death, **[Levey, 2007]**. Many low-income and middle-income countries are not able to deal with these serious long-term consequences. Given the high costs of treating ESRD, it is unsurprising that the provision of renal replacement therapies is virtually non-existent in many parts of sub-Saharan Africa, **[Grassmann, 2005]**. In all parts of Africa research funding is heavily skewed in favour of infectious diseases. This contributes to inadequate data on CKD and an overall low awareness among the public, healthcare workers and government, **[Luyckx, 2018]**.

The increased attention being given to CKD worldwide currently is attributable to several factors: the rapid increase in its prevalence, the enormous cost of treatment and hospitalisation, an appreciation of the role it plays in increasing the risk of cardiovascular disease, and the continued discovery of measures to slow its progression. However, despite the clear association with adverse outcomes, kidney disease has the lowest evidence base of any major medical specialty, with a recent systematic review struggling to find high quality randomised controlled trials from which to make effective recommendations, **[Strippoli, 2004]**.

Underlying risk factors for chronic kidney disease

CKD is a complex disease process with many aetiologies, where the cause, the presence of underlying risk factors and the stage of disease can dictate the rate of progression and loss of renal function. There are several primary risk factors involved in the progression of CKD including age, gender, race, family history, and stage of CKD, **[Kazancioğlu, 2013]**. Two separate large meta-analyses showed a progressive decline in renal function with increasing age, with over 10% of adults older than 65 years suffering from CKD3a or worse.

Also shown in these articles was that men exhibit a more rapid decline in GFR, with worse outcomes than women. This can most likely be attributed to gender-specific differences in glomerular structure, gene expression and the activity of local hormones and cytokines [Düsing, 2006]. Multiple studies have consistently shown that African descendants are at increased risk for CKD occurrence and progression to ESRD, [Peralta, 2010].

There are a number of independent risk factors, where optimal management, pharmacotherapeutic interventions and lifestyle modifications can be used to improve both renal and cardiac outcomes, [Nagata, 2011]. These risk factors, often considered to be modifiable, include diabetes, hypertension, dyslipidaemia, elevated body mass index (BMI), proteinuria, smoking and anaemia, [Levey, 2002 KDOQI]. The first five comprise a clustering of cardiovascular risk factors termed metabolic syndrome, which itself is regarded to be an independent risk factor for CKD occurrence, [Lea, 2008]. The three most highly studied factors that are linked to effects on eGFR are hypertension, proteinuria and the effect of therapies aimed at addressing these, [Pugh, 2019].

Hypertension is both a cause and a consequence of CKD. In a meta-analysis of 84 randomized and non-randomized trials in patients, for every 10mmHg drop in mean arterial pressure there was an improvement in rate of loss of GFR of 0.18 ml/min/1.73 m² per month, and a significant decrease in microvascular complications, [Saweirs, 2007]. The current recommendation for CKD patients suggests a target blood pressure (BP) of less than 135/80mmHg in most patients, and the interventional Systolic Blood Pressure Intervention Study (SPRINT) demonstrated a significant reduction in outcomes with intensive SBP control (<120) in high risk individuals, including CKD and for those with >1 g/day of proteinuria [Thomas, 2016].

Proteinuria is common in both diabetic and non-diabetic patients with CKD, and is a strong risk factor for disease progression [Cravedi, 2013]. In non-diabetic CKD, an 80% reduction in the relative risk of CKD progression per gram per day reduction in proteinuria has been demonstrated, [Jafar, 2011]. BP lowering will decrease proteinuria, however, some studies are able to show an effect of proteinuria reduction on CKD progression independent of BP control. This is because proteinuria often signifies an ongoing inflammatory or haemodynamic process and albumin itself is thought to be toxic to the tubules, [Bakris, 2008].

In a post hoc analysis of 273 patients with protein losing nephropathies, patients with the largest short-term reductions in proteinuria had the slowest declines in GFR, regardless of BP control, **[Ruggenenti, 2003]**.

Treatment with specific antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB); decreases MAP, reduces proteinuria and slows CKD progression, **[Jafar, 2001]**. In non-diabetic CKD, meta- analyses show that ACEI and ARB can reduce proteinuria, **[Casas, 2005]**. In diabetic CKD, meta-analyses demonstrate that ACEI in type 1 diabetics, and both ACEI and ARB in type 2 diabetics, decrease the probability of progression from micro- to macro-albuminuria, the progression to nephrotic syndrome and the rate at which renal dysfunction occurs.

Diabetic nephropathy is rapidly becoming the single most common cause of ESRD worldwide **[Luyckx, 2018]**. Multiple large studies separating patients into 'intensive' and 'conventional' insulin therapy groups, show the benefit of strict glycaemic control on proteinuria, as well as a definite reduction in microvascular end-points. In these trials, an HbA1c of <6.5% is suggested to prevent the onset and progression of diabetic microangiopathy, **[Hinzmann, 2012]**. The updated KDOQI guidelines for diabetes and CKD recommend an HbA1c of approximately 7%, **[Levey, 2002 KDOQI]**. The intensive group in these studies demonstrated a marked reduction in microvascular complications and progression, **[Patel, 2008]**. Thus the management of patients' needs to be optimized for the individual, in order to attain the necessary control as well as reducing complications.

The prevalence of obesity has been shown in multiple studies to be increasing at a highly alarming rate, with many black South African adults over the age of 20 meeting the clinical criteria for metabolic syndrome **[Peer, 2015]**. Central obesity has been directly linked to a two-fold increase in the development of CKD, with the Framingham Offspring Study demonstrating that an elevated BMI increased the odds of developing CKD by 23%, **[Fox, 2004]**. The effects of increased adiposity impact the kidneys directly via production of adiponectin, leptin and resistin, **[Kovesdy, 2017]**. These increase inflammation and oxidative stress, and are implicated in the development of focal segmental glomerulosclerosis and glomerulomegaly, and to the risk of progression to ESRD, **[Weisinger, 1974]**.

CKD is commonly associated with lipid abnormalities, and recently several lipid profile variables have been linked with the onset and progression of kidney disease **[Pandya, 2015]**. Studies show that in patients with CKD elevated total cholesterol, LDL-cholesterol and apolipoprotein B levels and lower HDL-cholesterol levels were all associated with more rapid decline in GFR, **[Pandya, 2015]**.

Uric acid (UA) is an oxidative metabolite of purine in humans, and plays a significant role in the development and progression of CKD **[Johnson, 2013]**. Various factors can affect the serum UA, including drugs and daily dietary intake, **[Li, 2014]**. Many large observational studies show a clear association between hyperuricemia and an increase in cardiovascular mortality, as well as an increased risk of adverse renal outcomes, including progression to ESRD in CKD patients, **[Bellomo, 2015]**. KNOW-CKD, a prospective cohort study, classified 2042 CKD patients into quartiles depending on their serum UA level. This study found the prevalence of advanced CKD was higher in patients with an increased UA level, **[Oh, 2019]**.

It is beyond any doubt that smoking is the number one preventable cause of death in most countries. It is also an important modifiable renal risk factor through mechanisms such as intrarenal vasoconstriction, and an increase in proinflammatory cytokines and oxidative stress. This ultimately leads to tubular dysfunction, tubular atrophy and glomerulosclerosis, **[Orth, 2008]**. Multiple studies document a clear association between smoking and CKD progression, **[Hallan, 2006]**. This includes effects on mediator systems that are known to be involved in the genesis of progressive renal damage, cardiovascular compromise, increasing proteinuria and an overall detrimental effect on renal outcomes, **[Orth, 2008]**. In addition it has been shown that smoking cessation before renal transplantation resulted in better graft survival when compared to graft recipients who had continued smoking **[Aref 2017]**.

Chronic anaemia is a common complication of CKD, and tends to worsen with progressive renal disease. Anaemia in CKD is often related to the direct decrease in erythropoietin (EPO) production, but can also be secondary to various factors such as effects of other chronic illnesses, to blood loss from haemodialysis and to nutrient deficiencies, **[Mikhail, 2017]**. Anaemia has been shown to contribute to disease progression through multiple ways such as, increased renal plasma flow, glomerular hyperfiltration, glomerulosclerosis and hypoxia of tubular cells with associated tubule-interstitial damage.

These mechanisms all contribute to worsening proteinuria, hypertension and ESRD. In the RENAAL study each 1 g/dl decrease in haemoglobin was associated with an 11% increase in the risk of ESRD, and multiple randomized studies have reported the renoprotective benefit associated with erythropoietin therapy, **[Gouva, 2004]**.

The two most common diagnoses obtained from biopsies of patients with HIV-CKD, are HIV associated nephropathy (HIVAN), occurring typically in young African adults with advanced disease, and HIV associated immune complex disease (HIVICK), **[Naicker, 2015]**. With the introduction of antiretroviral therapy, there has been a significant decline in the incidence of HIVAN **[Francois-Xavier, 2012]**. South African studies showed an improvement in renal function with ART irrespective of renal histology, with both HIVAN and HIVICK demonstrating a good response, **[Fabian, 2013]**. Progression to ESRD has been reported to be more likely when the following parameters are present; significant proteinuria, severely reduced GFR, hepatitis co-infection, diabetes mellitus and chronic interstitial fibrosis, **[Post, 2008]**. The DART study also showed an improvement of eGFR by 1.9 – 6 mL/min/1.73 m² after 4 – 5 years of ART, and an improvement in median eGFR by 21% in Ugandan HIV CKD patients after being on ART for 2 years, **[Reid, 2008]**.

II. STUDY SIGNIFICANCE AND RESEARCH AIM

Although often considered a complication of diabetes or hypertension, CKD has numerous complex causes and has a direct relationship with many other medical illnesses. It is associated with a tremendous economic burden, and an ever-increasing impact on national morbidity and mortality. Given the limited epidemiological data, the frequent lack of awareness and the poor access to health services, such numbers probably underestimate the true crisis posed by kidney disease.

The purpose of this retrospective study will be to identify and describe the relationship between several non-modifiable and modifiable risk factors, and the progression and outcomes of CKD in Black South African patients attending the Chris Hani Baragwanath Renal Outpatients Department. This is to appreciate how common each risk factor is and how effectively each is controlled within our population. It will also highlight the important role each of these factor plays in contributing to CKD outcomes, and ultimately to the significant problems associated with renal disease in our country, allowing us to make recommendations on the future care of patients.

III. SPECIFIC OBJECTIVES

1. To describe the demographics and the prevalence of associated modifiable and non-modifiable risk factors of renal disease in black South African patients registered in the Renal outpatient clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) at any point during 2010-2020, for a minimum follow-up period of four years.
2. To record the rate of decline in eGFR in CKD patients with stage 3-5 renal disease attending the outpatient clinic over a follow-up period of four years.
3.
 - A) To establish the level of control of risk factors in our patient population
 - B) To investigate how these risk factors impact on progression of CKD.
4. To determine the prevalence of the following CKD outcomes during the study period: admission rate, renal replacement therapy, cardiovascular disease (Coronary artery disease / Cerebrovascular accident), and death.

IV. METHOD

This will be a retrospective chart review study of patients with CKD stage 3-5, enrolled in the Renal outpatient clinic at CHBAH during the period 2010-2019, and with a minimum follow-up of four years for each patient. The estimated GFR will be calculated by the abbreviated modification of diet in renal disease (MDRD) equation, which takes into account the patient's age, race and gender [Levey, 2009].

Setting

Renal Outpatient Clinic at CHBAH.

Patient selection

Inclusion:

- All subjects with a history, clinical diagnosis and laboratory confirmation of with CKD.
- All subjects must be at stage 3-5 renal disease at presentation to the clinic
- All subjects must be of black African origin
- All subjects must be over 18 years old
- Patients required to be registered in the outpatient clinic at any point during time frame 2010–2020, for a minimum follow-up of four years.

Exclusion:

- Renal disease subjects visiting the renal unit for less than 4 years
- Stage 1 and 2 of CKD
- Subjects below 18 years old

Measurement and data collection

Epidemiological Data:

- Demographics (age, socio-economic status and gender) – race will not be assessed as all patients shall be of black African ethnicity

Clinic information:

- Initial age at presentation
- Duration that the patient has attended the clinic

CKD timeline measurements:

- Creatinine and eGFR at time 0 years (presentation)
- Creatinine and eGFR at time 2 years
- Creatinine and eGFR at time 4 years

Modifiable and non-modifiable risk factors:

- Smoking: non-smoker, ex-smoker, current smoker
- Anthropometry: height, weight, body mass index (value & category)
 - BMI calculation = $\text{weight} / (\text{height squared}) = \text{kg/m}^2$
 - BMI category
- Hypertension
- Hypercholesterolaemia
- Diabetes: no, yes (type 1 or type 2)
- Human immunodeficiency virus infection, no, yes (viral load suppression)

Medical therapy:

- ACEI: no, yes (compliance)
- ARB: no, yes (compliance)

Outcomes:

- Admissions
- Cardiovascular disease
- Renal replacement therapies (RRT) – dialysis and renal transplantation
- Death (month, year)

Progression data of risk factors at time 4 years

- Blood pressure
- HbA1c (%)
- BMI (kg/m²)
- Cholesterol (mmol/l)
- Urine PCR (mg/mmol), Urine dipsticks, Albumin (g/L)
- Haemoglobin (g/dL)
- Uric acid (mmol/l)

Sample size, statistical methods and data analysis

A sample size of 300 patients will be statistically significant to represent the 6000 patients currently attending the Renal Unit at CHBAH. This is achieved using a 95% confidence level and a 5% margin of error, (Qualtrics). The sampling will begin once study approval has been obtained and will continue until at least 300 subjects (meeting the inclusion criteria, and not meeting any exclusion criterion), have been collected. Data will be collated onto an Excel spreadsheet, and imported into SPSS Statistical Package for Social Sciences (SPSS) version 23.0 for analysis. A p value of 0.05 shall be chosen. Descriptive statistics, will include mean, median, range, standard deviation, variance and standard error. Data will be tested for normality and skewed data will be log transformed. Inferential statistics will thereafter be conducted, and reported on as conclusive finding in this cohort. Student T Test will be used to compare continuous variables and chi squared test to compare categorical variables. Multivariable logistic regression analysis will be used to determine principle risk factors for decline in GFR.

For Objective 1

- The demographic data will be described (age, social economic status and gender), including the age of onset and the duration of disease.
- The prevalence of risk factors from the data collected will be determined and described in the cohort; these include
 - smoking and BMI
 - hypertension, dyslipidaemia, diabetes, and retroviral disease

For Objective 2

- The MDRD equation will be used to calculate the eGFR (continuous data) of 300 subjects in the study at time 0 years, time 2 years and time 4 years.
- The eGFR will be used to calculate the CKD stage (categorical data) for 300 subjects at the study at time 0 years, time 2 years and time 4 years.
- Thereafter, the change in the eGFR and CKD stage from time 0 years to time 2 years, and from time 2 years to time 4 years will be calculated

For Objective 3

To explore risk factors:

- a. The level of risk factor control will be established in this cohort by measuring against the target value (calculated on Microsoft Excel with formulae):
 - i. Smoking – non-smoker or ex-smoker as compared to current smoking
 - ii. BMI – current BMI vs normal BMI
 - iii. Hypertension – target BP control (120/80 mmHg)
 - iv. Hypercholesterolaemia – target cholesterol (<4.5 mmol/l)**
 - v. Diabetes – target HbA1c of 7.0%**
 - vi. RVD – viral load suppression, normal CD4 count

** Several guidelines exist for the target level of cholesterol and HbA1c. For the purpose of this study we have used SEMDSA Guidelines, (SEMDSA, 2017)

Chronic kidney disease develops in many diabetic patients and anaemia is often a complicating factor. Hba1c can misrepresent glycaemic control in diabetic patients due to a low haemoglobin, and is understood to be a limitation in this subset of patients.

- b. The contribution of the modifiable and non-modifiable risk factors in the eGFR decline in black South African patients will be evaluated for
 - vii. The age of CKD onset
 - viii. The durations of CKD since onset (Duration of illness = age on July 2019 - age at onset of CKD)
 - ix. The relationship to the eGFR and the CKD changes at the time intervals

For Objective 4

The CKD outcomes will be (admission, cardiovascular disease, renal replacement therapy and death) where such information is available

- The prevalence of each of the outcomes will be described
- The mean eGFR will be compared between the groups with and without each outcome.
- Where possible, 4 year event rates, hazard ratios and survival rates will be calculated.

V. STUDY LIMITATIONS

Limitations identified in the study include:

- This is a retrospective chart review study which relies on accurate capture of relevant data.
- This is a 4 year analysis that reviews patients at the Renal Unit at CHBAH.
- Patients may belong to other hospitals in their catchment area, which may contribute to loss of valuable data such as loss of information regarding outcomes, especially in cases of death.
- The sample size chosen is statistically representative of the population, but remains subject to standard random sampling error.

VI. ETHICS

As this is a retrospective observational study there is no need to have direct participant contact or obtain informed consent from each patient for the use of his/her medical information.

- There will be no vulnerable groups (children, mentally disabled etc.) included in the study.
- Full anonymity and confidentiality
- Data protection and safe storage
- No notable conflicts of interest

To ensure complete ethical compliance the study protocol will be submitted to the Human Research Ethics Committee of the University of the Witwatersrand for approval.

Permission to conduct the study at CHBAH will be sought from the clinical superintendent of the Hospital and to review outpatient files from the Renal Head of the Department.

The medical staff at the renal outpatient clinic will also be informed.

VII. FEASIBILITY

A. Study funding

ITEM	ESTIMATED COST (R)	FUNDING
Travel	R1500.00	Dr S Maharaj
Photocopies	R1000.00	Dr S Maharaj
Printing	R1000.00	Dr S Maharaj
Stationary	R500.00	Dr S Maharaj
Total cost	R4,000.00	Dr S Maharaj

B. Timing

	May 2019	June 2019	July 2019	August 2019	Sep 2019	Oct 2019	Nov 2019	Dec 2019	Jan 2020	Feb 2020	March 2020	April 2020	May 2020
Literature review	x	x											
Protocol preparation		x	x										
Protocol assessment			x	x	x								
Ethics					x	x	x						
Data collection							x	x					
Statistical analysis								x	x				
Thesis write-up										x	x	x	
Thesis submission												x	x

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Appendix 2: KDIGO classification of CKD ^[1]

GFR Stages	GFR (mL/min/1.73 m²)	Terms
G1	>90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure
Albuminuria Stages	AER or ACR (mg/24 h or mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30–299	Moderately increased
A3	≥300	Severely increased

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate (24 hours).

Causes of CKD

1. Presence or absence of systemic disease and
2. Location within kidney of observed or presumed pathologic-anatomic findings such as glomerular diseases, tubulointerstitial diseases, vascular diseases, cystic and congenital diseases.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter Suppl* 2013;3:1–150.

Appendix 3: Nutritional status as defined by World Health Organisation (WHO) ^[2]

BMI measurement	Category
<18.5 kg/m ²	Underweight
18.5 - 25 kg/m ²	Normal
25 - 30 kg/m ²	Overweight
30 - 35 kg/m ²	Obese Grade I
35 - 40 kg/m ²	Obese Grade II
>40 kg/m ²	Obese Grade III

Appendix 4: Ethics Clearance



R14/49 Dr Shriyan Maharaj

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) **CLEARANCE CERTIFICATE NO. M200303**

NAME: Dr Shriyan Maharaj
(Principal Investigator)
DEPARTMENT: Internal Medicine
Chris Hani Baragwanath Academic Hospital
Renal Out Patients

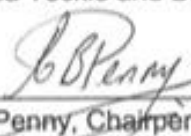
PROJECT TITLE: The risk factors for progression of chronic kidney disease in a cohort of South African black patients

DATE CONSIDERED: 27/03/2020

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Gloria Teckie and Dr Nasrin Goolam Mayhodeen

APPROVED BY: 
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/07/2020

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 **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 5: TURN-IT-IN Report

TURNITIN RESEARCH REPORT.pdf			
ORIGINALITY REPORT			
6%	6%	9%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS
PRIMARY SOURCES			
1	archive.org Internet Source		1%
2	www.ncbi.nlm.nih.gov Internet Source		1%
3	ndt.oxfordjournals.org Internet Source		1%
4	B M Brenner. "Predicting initiation and progression of chronic kidney disease: Developing renal risk scores", Kidney International, 11/2006 Publication		1%
5	escholarship.org Internet Source		1%
6	worldwidescience.org Internet Source		1%
7	www.dovepress.com Internet Source		1%
8	Aderemi B. Adeniyi, Carien E. Laurence, Jimmy A. Volmink, M. Razeen Davids. "Prevalence of		1%

Appendix 6: Data Collection Sheet

CASE NUMBER			
DEMOGRAPHICS			
Age:	Gender:	Employed:	
CLINIC INFORMATION			
Initial age at presentation:	Duration of clinic attendance:	Defaulted:	
CKD STAGE			
Presentation Time 0 Creatinine: eGFR	Time 2 years Creatinine: eGFR	Time 4 years Creatinine: eGFR	
MODIFIABLE and NON-MODIFIABLE RISK FACTORS			
Smoker	Ex-smoker	Non-smoker	
Height(cm)	Weight(kg)	BMI	
Hypertension	Yes	No	
Dyslipidemia	Yes	No	
Diabetes	Yes / No	T1	T2
Retroviral Disease	Positive	Negative	
MEDICAL THERAPY			
ACE-I Y / N	ARB Y / N	Compliant Y / N	
OUTCOMES			
Admissions	CVD	RRT	DEATH
FACTORS MEASURING RISK FACTOR CONTROL			
RISK FACTOR	TIME 0 YR	2 YR	4 YR
BP to target			
HbA1c (%)			
BMI (kg/m ²)			
Cholesterol (mmol/L)			
Haemoglobin (g/dL)			
HIV VL (copies/mL)			
Urine dipstix			
Urine PCR (g/mmol)			
Albumin (g/L)			
Uric acid (mmol/L)			

10. SUPPLEMENTARY MATERIAL AND DATA

Logistic regression method modelling causes of eGFR decline

The decline in eGFR for each of the 265 patients was first calculated over Time-0, Time-2 and Time-4, and the results were subsequently converted to percentage. Overall patients' renal function declined, with the average rate of decline in eGFR for all 265 patients over 4 years being 26%. We divided the 265 patients into those whose percentage decline in eGFR was higher than the average (i.e. they progressed at a faster rate), and those equal to or below the average and therefore performed better. Our study had 90 (34%) patients above the average, which is the outcome of interest we were building our model to predict.

We thereafter designed a model using demographics, risk factors and baseline creatinine to predict which patients would perform worse than the average in 4 years, using a logistic regression system. We began by performing an exploratory assessment first by using all the predictors in a univariate test against the outcome of below or above the average eGFR decline in the cohort of 265 patients. The regression model was fitted using the exploratory variables advanced after the univariate analysis, and this was followed by manual intelligent modelling.

Decline in eGFR - Exploratory variables

Categories		Decline in eGFR			p-value
		Above avg.	Below avg.	Total	
Gender					
• Male	51	93	144	0.90	
• Female	41	80	121		
Socio-economic					
• Unemployed	76	137	210	0.15	
• Employed	13	40	55		
Smoking					
• Non-smoker	60	112	172	0.05	
• Ex-smoker	16	47	63		
• Smoker	14	16	30		
Hypertension					
• No	18	27	45	0.15	
• Yes	71	149	220		
Dyslipidaemia					
• No	50	89	139	0.01	
• Yes	40	86	126		
Diabetes					
• No	61	101	162	0.02	
• Yes	26	77	103		
HIV					
• No	50	122	172	0.02	
• Yes	39	54	93		
Decline in eGFR	N	Mean (SD)	95% CI	p value	

Age (years)

Below	90	54.56 (12.15)	52.01 to 57.10	0.01
Above	175	58.33 (13.36)	56.35 to 60.30	
Combined	265	57.06 (13.07)	55.49 to 58.63	
Difference		-3.78	-7.08 to -0.47	

Creatinine

Below	86	296.22 (234.95)	247.01 to 345.43	0.00
Above	179	188.00 (79.33)	176.27 to 199.73	
Combined	265	224.34 (158.73)	205.26 to 243.43	
Difference		108.22	69.89 to 146.55	

[p<0.05 = statistically significant]

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Literature review (1 – 77)

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Appendices (1 – 2)

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