The association between renal sonography and renal function in chronic kidney disease

at Inkosi Albert Luthuli Chief Hospital

A retrospective descriptive study

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As the candidate's supervisor I have/have not approved this thesis for submission

Signed: [redacted] **Name:** A. Assounga **Date:** 09 September 2020

Declaration

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Dedication

To Kate and Gabi

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Table of contents

List of abbreviations

CD	Communicable Disease
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CG	Cockcroft-gault equation
CMD	Corticomedullary differentiation
DM	Diabetes Mellitus
eGFR	Estimate glomerular filtration rate
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HIV	Human Immunodeficiency Virus
HPT	Hypertension
IALCH	Inkosi Albert Luthuli Central Hospital
IE	Increased echogenicity
IN	Interstitial nephritis
KDIGO	Kidney Disease Improving Global Outcomes
KZN	Kwa-Zulu Natal
LCMD	Loss of corticomedullary differentiation
MDRD	Modified diet in renal disease equation
NCD	Non-communicable disease
NE	Normal echogenicity
OU	Obstructive uropathy
PKD	Polycystic Kidney Disease
RAS	Renal artery stenosis
RE	Retained echogenicity
RL	Renal length
RRT	Renal replacement therapy
RSA	Republic of South Africa
SEM	Standard error of the means
SLE	Systemic Lupus Erythematosus
US	Ultrasonography

List of tables, figures and appendices

Abstract

Background

Non-communicable diseases (NCDs) are rapidly emerging as a major cause of chronic kidney disease (CKD) in Africa with a reported prevalence of 10.7% locally. At current, few high-quality studies assessing the epidemiology of CKD in South Africa have been published. Alarmingly, CKD is now at epidemic proportions and is a leading cause of mortality with significant cost implications. This study aims to investigate economic means of predicting renal function in CKD by exploring the association between estimated glomerular filtration rate (eGFR) and renal morphology evaluated by ultrasound (US).

Methods

This is a retrospective descriptive chart review conducted at the Department of Nephrology, Inkosi Albert Luthuli Central Hospital (IALCH), Cato Manor, Kwa-Zulu Natal from January 2016 to December 2016. A total of 455 patients who had met the Kidney Disease Improving Global Outcomes (KDIGO) definition of CKD with eGFR (MDRD) and renal US performed were included. Demographic, clinical, laboratory and renal morphological data (renal length (RL), increased echogenicity (IE) and loss of corticomedullary differentiation (LCMD)) on US were collected and analyzed with SPSS software (*v*. 27). Associations between eGFR, parameters on US and CKD risk factors were determined using logistic regression analysis.

Results

Black Africans 75.2% (*n.*342) and females 56.9% (*n.*259) predominated the sample. Whilst, Indians, Whites and Coloureds comprised of 20.4%, 2.42% and 1.98% of the study respectively. The median age was 45.8 ± 14.3 years. Hypertension 34.9%, diabetes 26.8%, HIV 27.5% and glomerulonephritis 9.89% were the four most frequently reported risk factors, of which Black Africans comprised more than 50% of cases ($p < 0.001$). A significant proportion of patients 65.7% (*n.*307) had end-stage renal disease with a median eGFR of 14.4 ± 12.8ml/min/1.73m^2 ($p < 0.001$). The median right and left RL were short at 8.49 ± 2.16cm and 8.60 ± 2.20cm respectively. Black Africans were also found to have significantly shorter RLs and lower eGFRs ($p < 0.001$). The dual effect of IE and LCMD predisposed to significantly shorter RLs and lower eGFRs than in the presence of one or no abnormality on US ($p < 0.001$). IE [-9.29 OR; 95% CI (-13.8 - -4.77); $p < 0.001$] and RL [right: 5.02 OR; 95% CI (3.44 – 6.60); p 0.04; left: 5.11 OR; 95% CI (3.56 – 6.66); p 0.04] were found to be significant predictors of eGFR. HIV was the only risk factor found to be negatively associated with all determined measures of renal function, as well as the sole predictor of IE [2.31 OR; 95% CI (0.17 - 3.15); p 0.02].

Conclusion

The CKD epidemic is driven by the complex interplay between communicable (HIV) and NCDs (HPT/DM) and has emerged as an important public health and economic threat in Southern Africa. Africans are most vulnerable presenting with an advanced and accelerated disease course. GFR determination and US are inexpensive means of determining renal function particularly in resource limited settings. IE and RL are surrogate markers of renal function with an increased echogenic pattern being most predictive of renal dysfunction in CKD, particularly in HIV.

Chapter 2

Introduction and background

Chronic kidney disease (CKD) is defined by either abnormalities in kidney structure or function which persists for more than 3 months.[1] It remains a major cause of both morbidity and mortality affecting an estimated 500 million people globally. Unfortunately, due to the paucity of local studies and systematic reviews the true prevalence of CKD in Africa is not known.[2] Smaller local studies approximate the prevalence to be as high as 17.7% in Sub-Saharan Africa or 190 persons per million population in 2017.[2,3] This is certainly exacerbated by the surge in both communicable [Human Immunodeficiency Virus (HIV)] and non-communicable disease [Diabetes Mellitus (DM) and Hypertension (HPT)] epidemics.[2]

As the burden of CKD escalates so too will the cost of therapy and the management of long-term complications. This poses an insurmountable threat to the economy and public health system which sub-serves 84% of the 52 million people living in South Africa.[2] Once end-stage renal disease (ESRD) has been established renal replacement therapy (RRT) may be initiated if various criteria are satisfied. Nevertheless, CKD is an expensive affair with the cost of dialysis amounting to upwards of R200 000 per patient/year.[3] Intensive primary preventative measures are necessary to perturb the development of CKD, progression to ESRD and the need for RRT.

An armamentarium of biochemical and radiological investigations are available when investigating CKD. Ultrasonography (US) and the estimated glomerular filtration rate (eGFR) are common examples. US is an inexpensive and non-invasive tool that is free of both contrast media and radiation exposure. Utilizing B-mode imaging, US has the ability to accurately delineate renal anatomy, identify pathological changes and allow for invasive interventions such as biopsy.[4] It stands to reason as to why it is the imaging modality of choice for the kidneys especially in resource-limited settings.

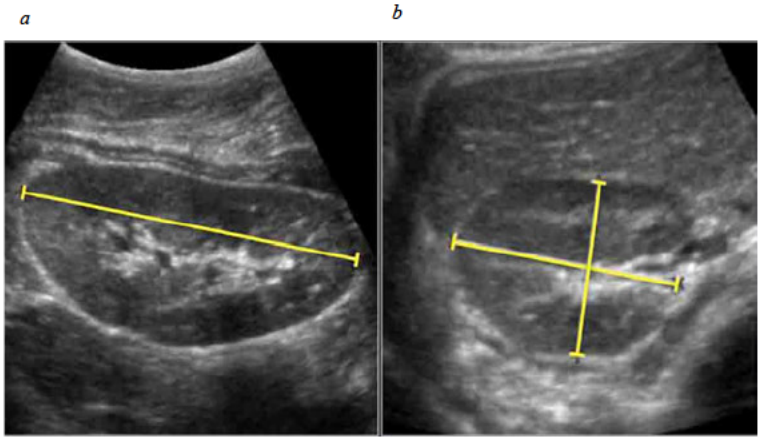

Figure 1 Longitudinal and transverse views of the right kidney using B-mode ultrasonography, Radiology assistant: https://radiologyassistant.nl/unsorted/normal-values-ultrasound
a. Bipolar length measurement with clear visualization of the cortex and medulla
b. Kidney width measurement calculated using the ellipsoid formula

Commonly reported renal anatomical parameters on US include length, parenchymal thickness, volume, echogenicity, corticomedullary differentiation and various vasculature indices. The collecting system and its configuration are also frequently reported when pathology is suspected distal to the renal pyramids.[5] The summation of the aforementioned parameters allows clinicians to determine the presence and reversibility of any pathological processes and assist in deciding on the most appropriate therapeutic intervention.[6]

Variations in kidney size are strongly associated with phenotype i.e., height and weight. Growth charts and anatomical variations in length, volume and thickness have been developed based on studies from non-African European populations.[7] These reference ranges may be inappropriate for the African population and could potentially lead to unnecessary investigations, invasive procedures and therapies.

Renal function may be estimated by either the use of the Cockcroft-gault (CG), Modified diet in renal disease (MDRD), or Chronic kidney disease epidemiology collaboration (CKD-EPI) equations. The eGFR is used to diagnose, stage and monitor response to therapeutic interventions.[8] It remains in contention that no formulae have been standardized for use in the African population. Furthermore, the yielded results vary greatly amongst the various formulae and may over or underestimate disease prevalence.[9] Additional studies reviewing equation performance and laboratory standardization in Africa are urgently needed. More accurate yet expensive and complex testing protocols exist involving radionuclides. However, such assays are costly and are not readily available in poorly resourced areas. Thus, making the estimation of GFR more attractive.[10]

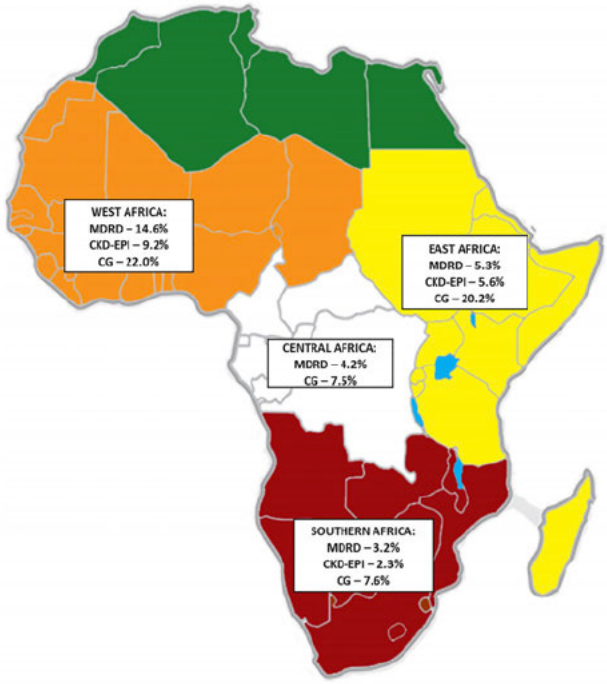

Figure 2 Summary of pooled prevalence of CKD determined by MDRD, CG and CKD-EPI in HIV populations of the African sub-regions, Ekrikpo UE, et al. (2018) Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. PLoS ONE 13(4): e0195443

Certainly, restricted access to laboratory and radiological services is a major concern, especially in rural areas. Such centers may have to rely on more feasible strategies for diagnosis and therapy. Defining key diagnostic tools for CKD in the African population will allow for the early identification of at-risk patients and the initiation of therapy. [11]

This study aims to review renal function (eGFR) and renal morphology on US of patients diagnosed with CKD at Inkosi Albert Luthuli Central Hospital (IALCH) to determine whether an association exists between these two variables. We also explore the epidemiology of CKD in this study.

Literature review and motivation

Chronic kidney disease (CKD) is the summation of various irreversible pathological processes affecting the nephron and accompanying renal compartments. It has been estimated that 100-200 patients per million population globally reach end-stage renal disease annually, of which 2% will be from Sub-Saharan Africa. CKD in low and middle-income countries is fuelled by the escalating burden of both communicable (CD) and non-communicable diseases (NCD). This places an immense amount of pressure on healthcare systems and the economy [1,2].

The burden of CKD in Kwazulu-Natal has been estimated at approximately 13%. The prevalence is projected to rise to epidemic proportions and apply undue strain upon an already struggling health care system. The South African Renal Society has outlined several key areas to address this apparent shortfall in the public provision of renal services. Interventions include improved primary care, management of risk factors and earlier referral of all patients with renal disease for specialist review[3,4].

Renal replacement therapy (RRT) is a scarce resource in South Africa. An estimated 168 patients per million population were initiated on RRT in 2014. Transplant is still infrequent with only 4 patients per million population receiving a graft in the same year. 90% of all patients undergoing dialysis are managed within the private health sector. Unfortunately, within the public health care sector, RRT is not as readily available. Patients with CKD would have to fulfil a 'clinical suitability for RRT criteria', which is decided upon by the department of health before being considered eligible for either dialysis or transplant. Cost is certainly a concern as sustaining a single patient on RRT can amount up to R 200 000 annually [5,6].

The department of health has initiated the campaign '25 by 2025' which aims to initiate 250 patients on dialysis and transplant 25 patients per million population by 2025. We however may be further from this goal than expected. The HIV and concurrent tuberculosis epidemics are still at large, with KZN being recognized as the epicentre. This double burden of disease is a major public health concern as resources may not be adequate to sustained care [7,8].

Cost-effective strategies are needed to perturb the high financial costs encountered in CKD. There are several methods that are commercially available to determine renal function. The estimated glomerular filtration rate (eGFR) is readily determined by the use of several formulae to diagnose, stage and assist in the guidance of therapy of patients on RRT [9].

Formal GFR determination via radioisotope assay is the most reliable and accurate method of determining renal function. However, it is expensive, requires trained technologists and is not readily

available in resource-limited settings. eGFR is thus the more attractive tool which estimates values based on age, gender and body surface area [9].

The Cockcroft-Gault (CG), the modification of diet in renal disease (MDRD) and Chronic kidney disease epidemiology collaboration (CKD-EPI) equations are widely recognized formulae used to estimate GFR. The association between renal function and size has been well described previously. Levey et al. noted a significant association between lower eGFR values and kidneys which were shorter and reduced in volume [10].

Renal imaging is essential in the management of CKD. Changes in anatomical structure provide important diagnostic and prognostic information. Ultrasonography (US) is the most common imaging modality utilized in clinical practice worldwide. It allows for excellent visualization of the kidneys and collecting system. Sonography is safe, non-invasive and more cost-effective when compared to other imaging modalities such as magnetic resonance. Some parameters assessed on US include renal length (RL), width and parenchymal echogenicity[11]. It is also an invaluable tool when undertaking invasive procedures such as renal biopsies [12].

RL is the distance between the inferior and superior poles of the kidney and is measured in the longitudinal axis view. RL has been reported to strongly correlate with anthropometric measurements i.e. height and weight. Normal renal length is 10-12cm. The former range has been determined from population-based studies on patients of European descent. Similar studies are yet to be conducted in the African population. Cortical thickness is measured from the base of the medullary pyramid to the edge of the kidney. The average cortical thickness is 7-10mm [11]

Parenchymal echogenicity is a measure of irreversible renal sclerosis and is determined by the amount of sound waves reflected back onto the US probe. When increased, an echogenic pattern correlates with interstitial fibrosis, tubular atrophy and glomerular sclerosis. Whilst a decreased echo pattern reflects possible renal oedema [11].

Change in renal structure indicates nephron loss. Many studies have reported on the strong relationship between renal function and morphological parameters on imaging [13]. Reshaid et al. performed a sonographic assessment of renal size in healthy adults. They had reported a mean left and right RL of 10.68 ± 1.4cm and 10.71 ± 1.0cm respectively. It was also found that there was no significant difference in RL or cortical thickness in the various age categories despite an age-related decline in glomerular filtration rate. It was thus concluded that any change in renal morphology should be considered abnormal [14].

Takata et al. found a stepwise negative correlation between cortical and parenchymal thickness, RL and GFR. This finding was most profound in the early stages of CKD. It was deduced that measurements obtained on ultrasound my assist in staging patients with CKD[15].

A similar result was reported by Adibi et al. in a cross-sectional study on healthy children. The sonographic assessment was performed by experienced radiologists whilst an eGFR was determined by using the Schwartz formula. A significant correlation was found between the aforementioned parameters amongst children[16].

Zanoli et al. assessed the correlation between US and renal function in hospitalized elderly patients. Renal length and anteroposterior diameter on US as well as the serum creatinine were determined. It was concluded that both length and volume correlated with GFR [17].

The sonographic features of CKD have been widely documented. Features include small kidneys, thin cortices and the presence of cysts. A normal cortical echo pattern may be encountered in CKD, however, the converse is more frequent. Therefore, the reliability of echogenicity has been questioned. Lucisano et al. reported that the association between sonographic parameters and eGFR are strengthened with anthropometric adjustment. Riagalleau et al. reported that large kidneys predict impending CKD [18,19,20]

Specific sonographic characteristics of the various risk factors implicated in the pathogenesis of CKD have been described. However, there is a paucity of local registry data examining the prevalent causes of CKD. In a cross-sectional study of 302 patients, it was found that Hypertension, diabetes and HIV were the most prevalent causes of CKD at primary/regional healthcare facilities in KZN [21]

In both type 1 and type 2 Diabetes Mellitus there is an increase in renal volume which parallels an increase in GFR values due to hyperfiltration. Maidan et al. studied the renal sonograms of type 2 diabetics. Individuals without overt hyperfiltration had normal kidneys whilst others had variable RLs with cyst formation. As compared to individuals with overt nephropathy, kidney sizes were noted to be considerably smaller reflecting the progressive glomerulosclerosis in end-stage diabetic nephropathy[22].

Hypertensive kidney disease is an important cause of CKD worldwide. Classically shrunken kidneys are a feature in hypertensive nephrosclerosis. In a prospective study performed by Egberongbe et al. evaluating renal volume on US in hypertensive kidney disease, it was concluded that no correlation existed between kidney size and the duration of hypertension. Similarly, Raman et al. reported comparable results in a cross-sectional community-based study [23,24].

Manifestations of renal disease in HIV are heterogeneous. HIV associated nephropathy (HIVAN) is characterized on US by a variable RL, globular shape, a LCMD, IE and decrease in renal sinus fat. Weerakkody et al. advocated in favour of the strong diagnostic ability of IE and LCMD on US in HIVAN [25,26]. Similar findings were noted by Atta et al. and N'Gbesso et al. Interestingly the latter study also found a strong correlation between RL and CD4 count [27,28].

It is most likely that similar correlations exist in our setting. Thus, this study aims to determine if a correlation exists between the glomerular filtration rate and renal morphology on sonography. Its clinical relevance will add to the vast body of pre-existing literature. Also, further correlations as to which aetiology best corresponds change in renal function to a specific morphological parameter on sonography may be determined and compared to other aetiologies. Such correlations may help clinicians determine either the renal morphology or functional state when either investigation is unavailable.

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Chapter 3: Methods

Research question

Determine if an association exists between renal morphological parameters on US (length, parenchymal echogenicity and corticomedullary differentiation) and renal function (eGFR) in CKD.

Objectives

1. Assess the prevalence of CKD and associated risk factors at IALCH
2. Assess the eGFR of patients at the Department of Nephrology, IALCH
3. Assess renal US performed on patients at the Department of Nephrology, IALCH
4. Determine if an association exists between eGFR and renal US i.e., renal length (RL), corticomedullary differentiation (CMD) and parenchymal echogenicity
5. Determine which US parameter best associates to eGFR according to CKD risk factor

Study Design

A retrospective descriptive review of Medical records. It is an analytic research design.

Site details

IALCH is an academic institution in Cato Manor, Durban, KwaZulu-Natal, South Africa. It provides quaternary medical care to several regional and district medical facilities within the province as well as the Eastern Cape. The department of adult Nephrology and hypertension provides specialist diagnostic and therapeutic care to patients aged 12 years and above presenting with a multitude of renal pathologies.

It is at this central point that the suitability for the initiation of RRT is determined for all patients within the public sector with CKD. Patients are then subsequently referred to various other regional 'dialysis capable' institutions to continue RRT and are reviewed at IALCH once every 6-12 months.

Historically, nephrology services have been centralized in Kwa-Zulu Natal. Specialist care and RRT was largely inaccessible to rural inhabitants. In order to resolve this inequity, the Department of Health has opted to decentralize renal care within the province. Dialysis teams now exist at most regional institutions. IALCH remains as the academic center subserving a significant proportion of patients. We recognize that IALCH may only encounter a fraction of patients with CKD in the province. However, the patient burden remains significant and continues to escalate.

Study enrolment

The study enrolled all patients aged 12 years and older diagnosed with CKD from January 2016 to December 2016. The source of enrolment was the database at the Department of Nephrology, IALCH. Data and information collected were correlated to the clinical records of the enrolled subjects. Patients who had appeared twice in the database for whatever reason were enrolled only once in the study.

Inclusion criteria

1. Patients diagnosed with CKD
2. Patients aged 12 years and older at the time of diagnosis
3. Both males and females were enrolled in the study
4. Patients managed as either out or inpatients
5. Patients required both renal US and an eGFR

Exclusion criteria

1. Any patient who did not meet the above requirements

Sample size

The sample size is based on estimating the correlation coefficient with a level of precision defined by a confidence interval around the correlation coefficient. A precision of ± 0.15 is considered sufficient for this study. Therefore, a minimum sample size of 281 is needed to estimate the correlation to within ± 0.15 ($0.1 \leq r \leq 0.4$) with a probability of 95%. This study comprised of 455 cases.

Data source, collection and analysis

The study procedures were limited to the review of existing medical records. Data was sourced and recorded (Appendix 1) from the IALCH electronic record keeping system (MEDITECH electronic health record-system). Enrolled patients were assigned a unique case number to ensure patient confidentiality.

Data collected

Demographic information: age, race (Black African, White, Indian and Coloured) and gender.
Aetiology: causative risk factors of CKD (HPT, DM, HIV)
Renal US morphological parameters: RL, parenchymal echogenicity and CMD. Renal width and volume were never reported in this study.
Renal function: Determined by eGFR (MDRD).

Definitions

CKD (KDIGO): abnormalities of kidney structure or function, present for >3 months, with implications for health and requires one of two criteria documented or inferred for >3 months: either GFR <60 ml/min/1.73 m^2 or markers of kidney damage, including albuminuria.

Renal length: measured on US as the longest diameter obtained on a posterior oblique image.

Echogenicity: indicates irreversible kidney damage i.e. glomerular sclerosis, tubular atrophy, focal leukocyte infiltration, fluid retention or arteriosclerosis. It is evaluated by comparing the echogenicity of the renal cortex, medulla and pyelic sinus with that of the adjacent liver and spleen (assuming that the liver and spleen are of normal echogenicity).

Corticomedullary differentiation: The cortex and medulla are visually distinct compartments of the kidney on US. This distinctive characteristic is lost in CKD due to progressive sclerosis. It is irreversible.

eGFR: The glomerular filtration rate is the volume of fluid filtered from the glomerular capillaries into the Bowman's capsule per unit time. A number of formulae have been devised to estimate this rate. The Modification of Diet in Renal Disease Study equation (MDRD) as noted below is the method utilized in this study:

$$eGFR = 32788 \times [Serum\ Creatinine]^{-1.154} \times Age^{-0.203} \times [1.212\ if\ Black] \times [0.742\ if\ Female]$$

Statistical analysis

Categorical data were summarised by frequencies and percents. Numeric data were examined for normality using histograms, box plots and the Shapiro Wilk test. Data meeting the assumption of normality was analysed using parametric statistics such as mean and standard deviation. Otherwise, nonparametric statistics were used i.e. median and interquartile range. This data was also categorised into groups for purposes of analysis.

Risk factors associated with CKD were identified by the Chi-Square /Fisher's exact tests for categorical data. T-tests or Wilcoxon rank-sum tests were used to compare numeric data. Risk factors significant at $p < 0.05$ were included in a logistic regression model to determine independent predictors associated with CKD.

The association between eGFR and renal US i.e. length and echogenicity were assessed initially by Pearson's/Spearman's correlation. A linear or ordinal regression model was used to quantify the relationship between the variables and to identify any factor affecting these relationships. A p-value <0.05 was considered statistically significant.

Data were analysed using the IBM Statistical Package for Social Sciences for Macintosh, version 27, Armonk, NY: IBM Corporation.

Ethical Consideration

Approval of research was obtained from the Department of Health (reference: 334/17) and the Biomedical Research Ethics Committee, University of Kwazulu-Natal (reference BE017/17) on the 28 August 2017.

Chapter 4 Results

Table 1 Clinical, radiological and laboratory characteristics

	Total	Male	Female	*p*
n.	455	196 (43.1%)	259 (56.9%)	<0.001
Age (years)				
Mean	45.8±14.3	44.6±13.1	46.7±15.1	0.20
SEM	0.67	0.94	0.94	
Min-Max	13-88	17-83	13-88	
Race				
African	342 (75.2%)	146 (32.1%)	196 (43.1%)	0.02
Indian	93 (20.4%)	39 (8.57%)	57 (12.5%)	0.12
White	11 (2.42%)	8 (1.76%)	3 (0.66%)	0.27
Coloured	9 (1.98%)	3 (0.66%)	6 (1.32%)	0.20
p	<0.001	0.24	0.24	
CKD aetiologies/risk factors				
Hypertension	159 (34.9%)	75 (16.5%)	84 (18.5%)	0.03
HIV	125 (27.5%)	46 (10.1%)	79 (17.4%)	0.16
Diabetes Mellitus	122 (26.8%)	54 (11.9%)	68 (14.9%)	0.07
Glomerulonephritis	45 (9.89%)	15 (3.30%)	30 (6.59%)	0.20
Obstructive uropathy	7 (1.53%)	6 (1.31%)	1 (0.22%)	0.39
Polycystic kidney disease	4 (0.88%)	2 (0.22%)	2 (0.22%)	-
Renal artery stenosis	1 (0.22%)	1 (0.22%)	0	0.50
Interstitial nephritis	1 (0.22%)	1 (0.22%)	0	0.50
p	0.03	0.04	0.04	
Kidney US: morphological features				
Echogenicity				
Normal	112 (24.6%)	50 (10.1%)	62 (13.6%)	0.09
Increased	343 (75.4%)	146 (32.1%)	197 (43.4%)	0.70
p	0.30	0.28	0.31	

Corticomedullary differentiation					
	Retained differentiation	131 (28.8%)	58 (12.7%)	73 (16.0%)	0.42
	No differentiation	324 (71.2%)	138 (30.3%)	186 (36.9%)	0.74
	p	0.26	0.25	0.26	
Length (cm)					
Right					
	Mean	8.49±2.16	8.60±2.44	8.40±1.93	0.01
	SEM	0.10	0.17	0.12	
	Min-Max	4.50-21.00	4.50-21.00	5.00-18.80	
Left					
	Mean	8.60±2.20	8.77±2.52	8.47±1.93	0.01
	SEM	0.10	0.18	0.12	
	Min-Max	5.00-24.90	5.00-24.90	5.00-16.70	
	p (Right vs. Left)	<0.001	<0.001	<0.001	
eGFR (MDRD)					
	Mean	14.4±12.8	15.2±13.1	13.3±12.4	0.04
	SEM	0.60	0.88	0.81	
	Min-Max	2.00-60.00	2.00-60.00	2.00-60.00	
CKD stages *(GFR: ml/min/1.73m^2)*					
	Stage 1 >90	0	0	0	-
	Stage 2 60-90	4 (0.88%)	2 (0.44%)	2 (0.44%)	-
	Stage 3 30-59	56 (12.3%)	8 (3.96%)	9 (8,35%)	0.04
	Stage 4 15-29	88 (19.3%)	37 (8.13%)	51 (11.2%)	0.01
	Stage 5 <15	307 (67.5%)	139 (30.5%)	168 (36.9%)	<0.001
	p	<0.001	<0.001	<0.001	
Number of patients on RRT		121 (26.5%)	40% (33.1%)	81 (66.9%)	0.10

Results continued

The clinical, radiological and laboratory characteristics of the study are presented in Table 1. The study comprised of 455 patients all of whom had met the KDIGO diagnostic criteria for CKD. Females predominated the sample over males at 56.9% (*n.*259) and 43.1% (*n.*196) respectively (p <0.001). The median age was 45.8 ± 14.3 years. Females were found to be older than males with a median age of 46.7 ± 15.1 years and 44.6 ± 13.1 years respectively (p = 0.20).

The racial distribution of the study consisted of 75.2% (*n.*342) Africans (black), 20.4% (*n.*93) Indians, 2.42% (*n.*11) Whites and 1.98% (*n.*9) Coloureds (p <0.001).

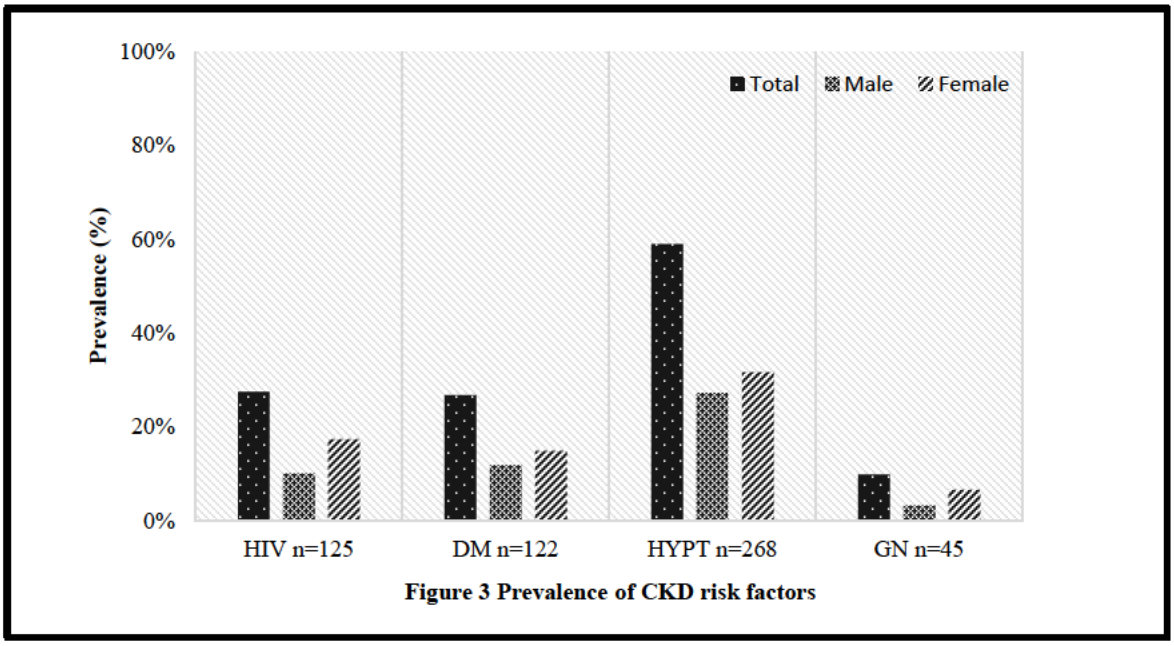

Figure 3 Prevalence of CKD risk factors

Hypertension (HPT) 34.9% (*n.*159), HIV 27.5% (*n.*124), Diabetes (DM) 26.8% (*n.*122) and Glomerulonephritis (GN) 9.89% (*n.*45) were the four most frequently reported risk factors of CKD (Figure 3). Renal artery stenosis (RAS), obstructive uropathy (OU), interstitial nephritis (IN) and polycystic kidney disease (PKD) contributed to 2.85% (*n.*13) of the total cases. No predilection was observed between gender and risk factors (p >0.50). The prevalence of diabetes increased with age, whilst the converse was seen in HIV and glomerulonephritis. Hypertension remained prevalent across all age groups (p <0.001) (Figure 4).

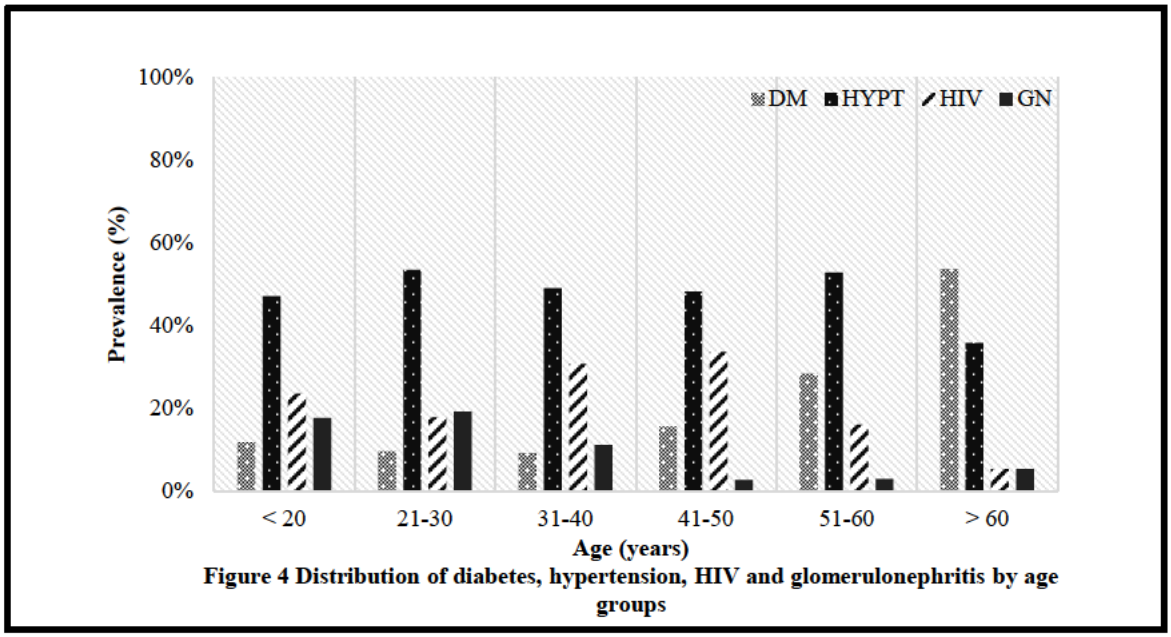

Figure 4 Distribution of diabetes, hypertension, HIV and glomerulonephritis by age groups

(Figure 12) A significant difference in the distribution of risk factors across racial groups had revealed that Africans comprised of more than 50% of the total cases in the HIV 98.4% (*n.*123), diabetes 53.3% (*n.*65) and glomerulonephritis 77.8% (*n.*35) groups (p <0.001).

Lupus nephritis 53.3% (*n.*24), focal segmental glomerulosclerosis 37.8% (*n.*17) and Hepatitis B 8.89% (*n.*4) were the most commonly diagnosed glomerulonephritides (other than HIV). The seven cases of obstructive uropathy were attributed to schistosomiasis (*n.*5), prostatic cancer (*n.*1) and a urethral stricture (*n.*1).

Method of reproducibility (Table 2)

Interobserver agreement was analyzed regarding the sonographic renal morphological parameters. The interclass correlation coefficient indicated an excellent interobserver agreement for echogenicity, CMD and RL for both the left and right kidney.

Table 2 Interobserver estimates of intraclass correlations for quantitative measurements

	ICC	95% CI		*p*	Interobserver agreement
		Lower	Upper		
Sonographic parameters	0.90	-0.02	0.22	<.001	Excellent

ICC, intraclass correlation coefficient

Renal parameters

A preponderance of pathological renal morphological changes was found sonographically. An increased renal echogenic pattern and LCMD was noted in 74.5% (*n.*343) and 71.2% (*n.*324) cases respectively. A statistically significant difference in both CMD and parenchymal echo pattern was noted between the race groups (p <0.001). Black Africans comprised 61.3% (*n.*279) and 58.7% (*n.*267) of the total IE and LCMD groups respectively. Conversely, a similar significant difference was not found between males and females (IE p = 0.70; LCMD p = 0.74).

Sonographic RLs are depicted in Figure 5. There was a statistically significant difference between the mean right and left RL (8.49 ± 2.16cm and 8.60 ± 2.20cm respectively) (p <0.001).

Males had larger RLs than females (right 8.60 ± 2.44cm; left 8.77 ± 2.52cm) and (right 8.40 ± 1.93cm; left 8.47 ± 1.93cm) respectively (Figure 5). This difference was significant (p <0.001). A Gender difference in median RL across all age groups was not found (right kidney p = 0.69; left kidney p = 0.36).

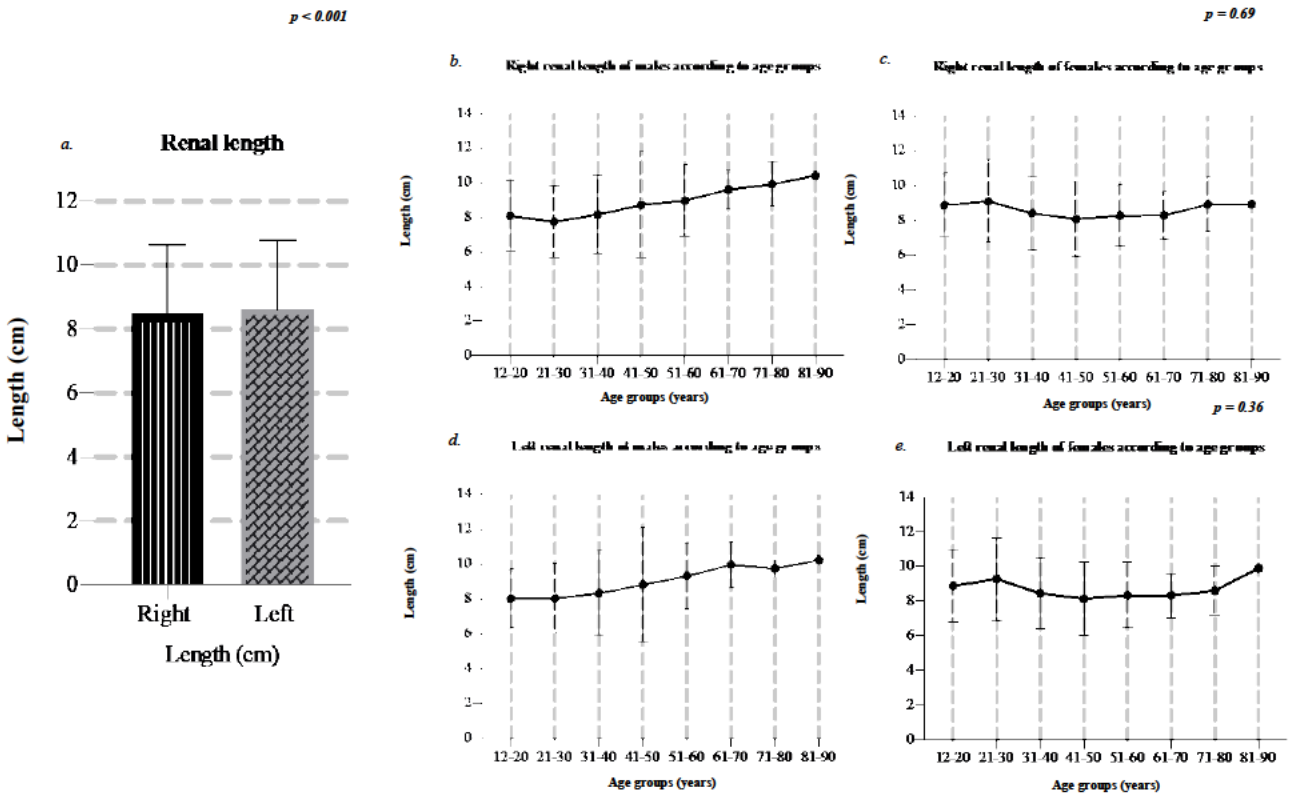

Figure 5 Comparison of renal length between:
a. Right and left kidney (8.49 ± 2.16cm and 8.60 ± 2 20cm respectively) ($p < 0.001$)
b.- e. Gender distribution between right ($p = 0.69$) and left ($p = 0.36$) renal length across age groups

Racial evaluation of RL had shown consistently longer kidneys in Whites (right 8.96 ± 2.64cm; left 8.79 ± 2.33cm), Coloureds (right 8.80 ± 1.98cm; left 8.86 ± 1.78cm) and Indians (right 8.72 ± 1.98cm; left 8.85 ± 1.97cm). Africans were noted to have shorter RLs (right 8.40 ± 2.20cm; left 8.52 ± 2.27cm) (right: p = 0.02; left: p = 0.04).

Longer RLs were observed in PKD (right 18.4cm ± 2.00cm; left 18.3 ± 4.47cm), OU (right 13.5 ± 2.89cm; left 13.5 ± 2.90cm) and DM (right 9.51 ± 1.58cm; left 9.65 ± 1.60cm). Whereas shorter RLs were consistent with HIV (right 8.44 ± 1.63cm; left 8.56 ± 1.74cm), GN (right 8.42 ± 2.15cm; left 8.48 ± 2.14cm) and chronic HPT (right 7.97 ± 2.38cm; left 8.08 ± 2.40cm) (p <0.001) (Figure 6).

IE portended to shorter RLs (right 8.02 ± 2.06cm; left 8.16 ± 2.14cm) when compared to kidneys with a normal parenchymal echo pattern (right 9.90 ± 1.83cm; left 9.95 ± 1.78cm) (p <0.001). Similarly, RLs were noted to be shorter (right 8.00 ± 2.07cm; left 8.13 ± 2.15cm) when accompanied by a LCMD and longer when CMD was retained (right 9.70 ± 1.90cm; left 9.74 ± 1.88cm). The dual effect of both an increased echogenic renal pattern and a LCMD on the kidney had resulted in significantly shorter

RLs (right 7.99 ± 2.07cm; left 8.13 ± 2.16cm) when compared to their counterparts with only one or none of the above-mentioned morphological abnormalities present (p <0.001) (Figure 7).

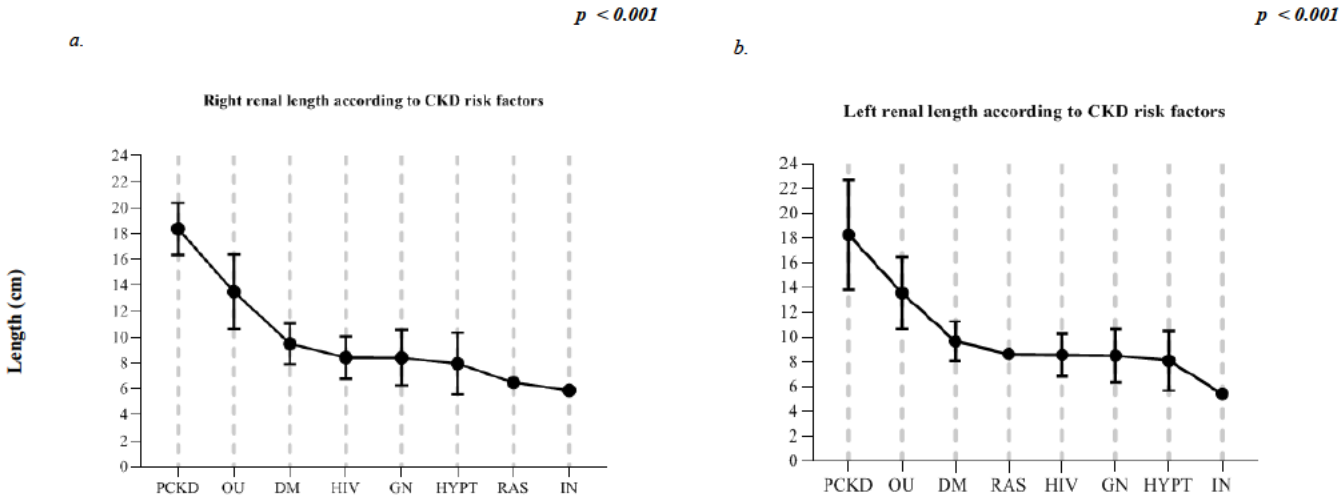

Figure 6 Distribution of right (*a.*) and left (*b.*) renal lengths across CKD risk factors

Longer kidneys noted in PKD, OU and DM vs. significantly shorter kidneys in HIV, GN and HPT (p <0.001)

HIV Human Immunodeficiency Virus, DM Diabetes Mellitus, HPT Hypertension, RAS Renal artery stenosis, OU Obstructive uropathy, IN Interstitial nephritis, PKD Polycystic kidney disease, GN glomerulonephritis, NE normal echogenicity, RCMD retained corticomedullary differentiation, IE increased echogenicity, LCMD lost corticomedullary differentiation

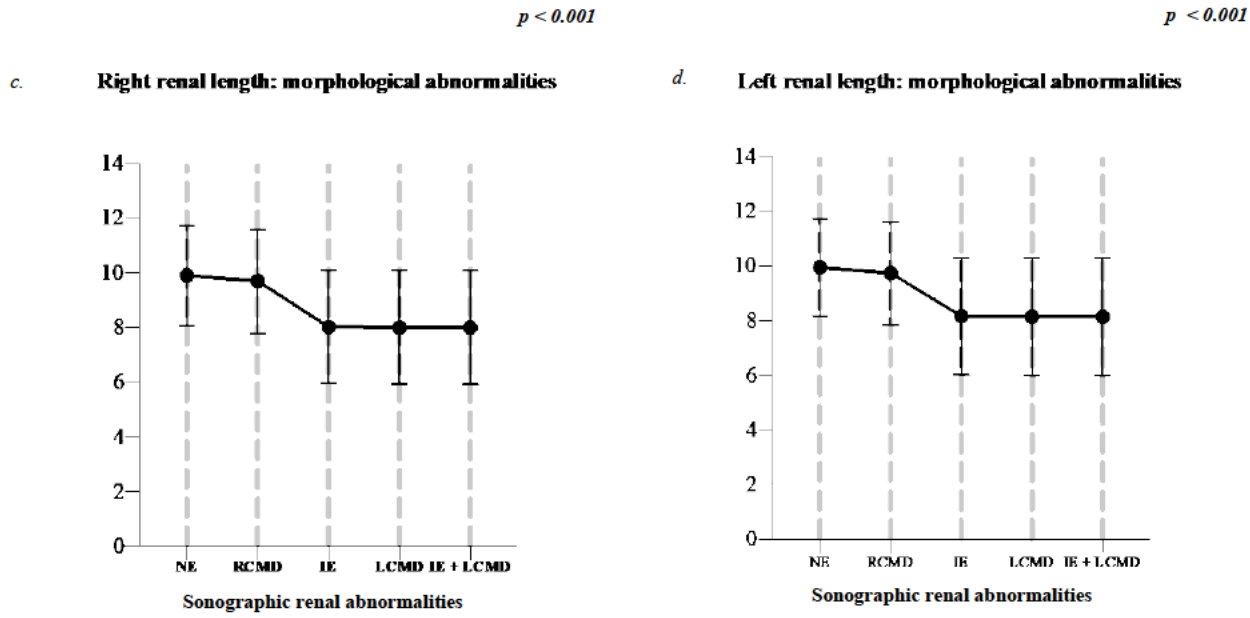

Figure 7 Distribution of renal sizes in the presence of US abnormalities

Significantly shorter lengths noted in the presence of abnormalities i.e., IE, LCMD or both (p <0.001)

US Ultrasound, HIV Human Immunodeficiency Virus, DM Diabetes Mellitus, HPT Hypertension, RAS Renal artery stenosis, OU Obstructive uropathy, IN Interstitial nephritis, PKD Polycystic kidney disease, GN glomerulonephritis, NE normal echogenicity, RCMD retained corticomedullary differentiation, IE increased echogenicity, LCMD loss of corticomedullary differentiation

Renal function (Figure 8)

A significant proportion of cases 67.5% (*n*.307) were noted to have end-stage CKD (GFR < 15ml/min/1.73m^2) (p <.001). The median eGFR was 14.4 ± 12.8ml/min/1.73m^2. The median eGFR of males and females was 15.2 ± 12.4ml/min/1.73m^2 and 13.3 ± 13.1ml/min/1.73m^2 respectively (p = 0.04).

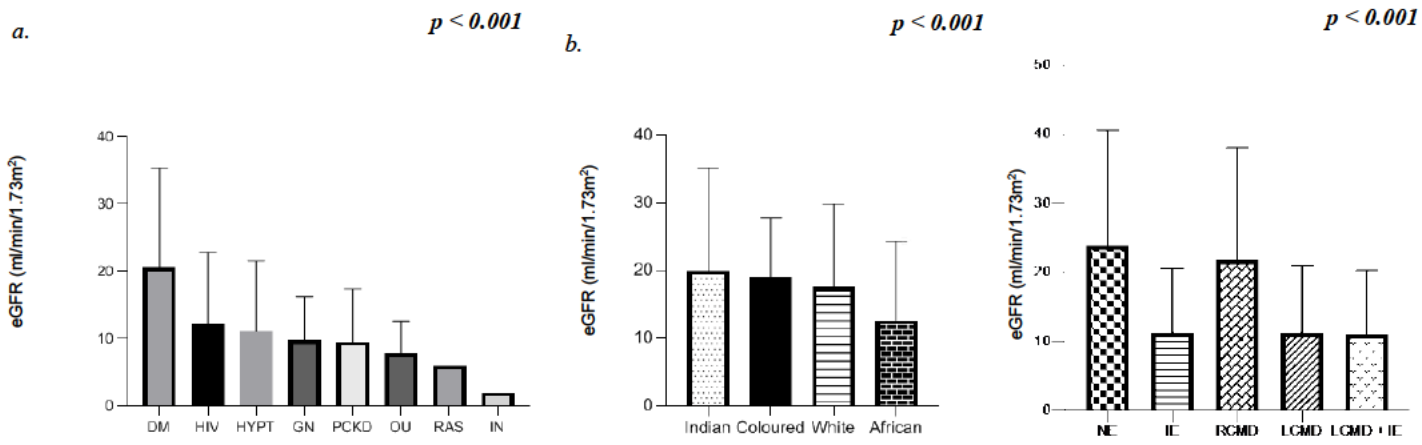

Figure 8 Distribution of eGFR (MDRD) across a. CKD risk factors b. racial groups c. sonographic abnormalities (Median and interquartile range)

HIV Human Immunodeficiency Virus, DM Diabetes Mellitus, HPT Hypertension, RAS Renal artery stenosis, OU Obstructive uropathy, IN Interstitial nephritis, PKD Polycystic kidney disease, GN glomerulonephritis, NE normal echogenicity, RCMD retained corticomedullary differentiation, IE increased echogenicity, LCMD loss of corticomedullary differentiation

Africans had a noticeably lower eGFR values of 12.6 ± 11.7ml/min/1.73m^2 in comparison to Indians, Coloureds and Whites who had statistically significant higher values of 19.9 ± 15.2ml/min/1.73m^2, 19.0 ± 8.77ml/min/1.73m^2 and 17.5 ±12.2ml/min/1.73m^2 respectively (p <0.001).

Hypertensives were found to have a lower median eGFRs of 11.1 ± 10.5ml/min/1.73m^2 than non-hypertensives and diabetics had higher eGFRs 20.6 ± 10.7ml/min/1.73m^2 than non-diabetics (p <0.001). No further statistically significant difference in renal function was found between the other studied risk factors of CKD (p >.05).

Kidneys noted to have morphological abnormalities on US revealed consistently lower eGFRs. A normal renal echo pattern and retained CMD noted eGFRs of 23.9 ± 16.7ml/min/1.73m^2 and 21.8 ± 16.2ml/min/1.73m^2 respectively. This contrasted the lower ranges noted with an increased echogenic pattern 11.3 ± 9.31ml/min/1.73m^2, LCMD 11.4 ± 9.58ml/min/1.73m^2 or both morphological abnormalities 11.1 ± 9.15ml/min/1.73m^2 (p <0.001).

Association between renal morphological measurements and estimated renal functions

Univariate and multivariate regression analysis using eGFR (MDRD), renal length, CMD and IE as dependent variables was performed to identify independent predictors for the abovementioned variables. Univariate regression analysis had identified significant associations between eGFR and US parameters (Figure 9). Note that only the right RL regression analysis is reported in this section as results were in close approximation to the left.

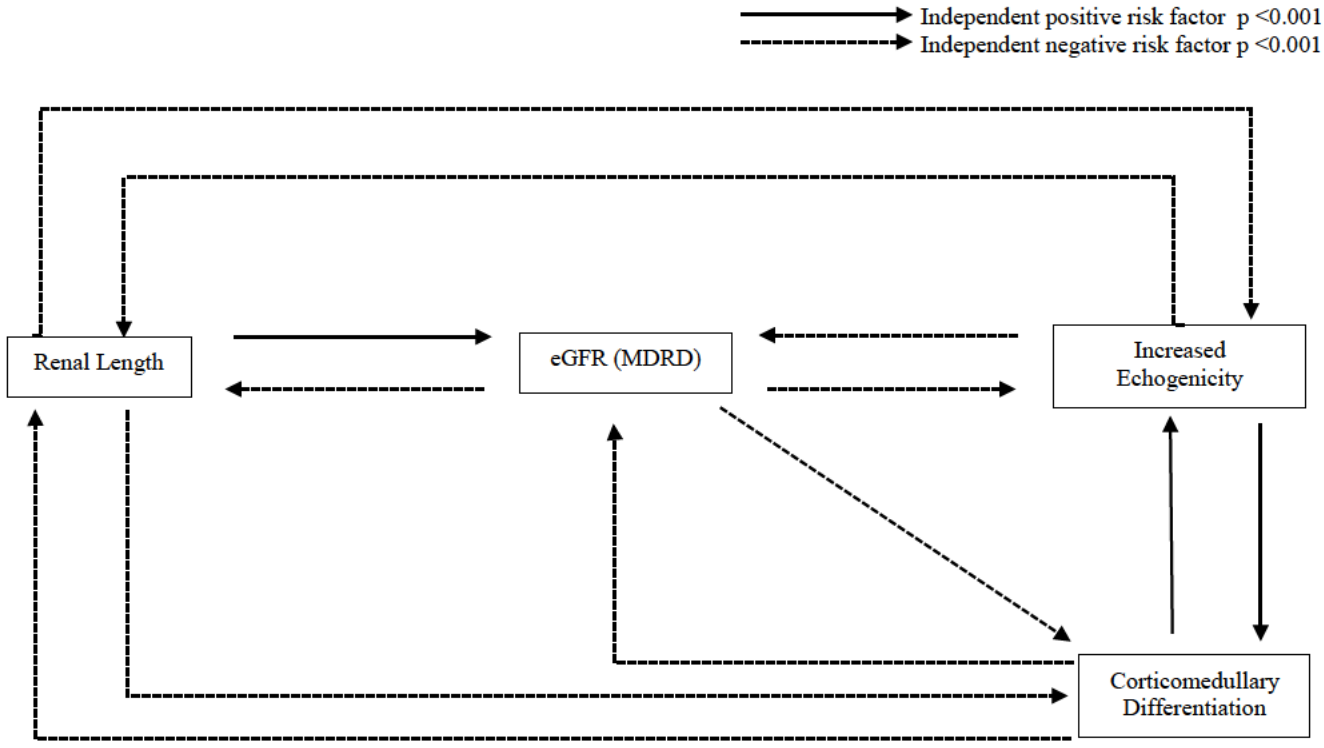

Figure 9 Associations between eGFR (MDRD) and US parameters as determined by univariate analysis
All associations were found to be very significant (*p <0.001*). Comparable results were found after multivariate analysis when controlled for age, race and gender. However, loss of corticomedullary differentiation was only associated with an increased echogenic pattern and shorter renal length with a concomitant loss of significance within the eGFR model.
eGFR Estimated glomerular filtration rate, MDRD Modification of Diet in Renal Disease Study equation, US Ultrasonography

An increased echogenic pattern [-12.6 OR; 95% CI (-15.1- -10.1); p <0.001] and LCMD [-10.5 OR; 95% CI (-12.9 - -8.05); p <0.001] were noted to be significant negative independent risk factors of eGFR. Whilst longer kidneys [1.32 OR; 95% CI (1.11 – 1.86); p <0.001] were associated with higher eGFRs (Table 4a). Similarly, the presence of US morphological abnormalities (IE [-1.87 OR; 95% CI (-2.30 - -1.44); p <0.001] and LCMD [-1.70 OR; 95% CI (-2.11 - -1.29); p <0.001]) were identified as significant negative independent risk factors for longer RLs whilst the conserve was seen with higher eGFR values [3.80 OR; 95% CI (1.09 – 6.05); p <0.001] (Table3a/b).

a.

	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*P*
		Lower	Upper			Lower	Upper	
Age	0.26	0.18	0.34	<0.001				
Race	0.34	2.01	4.68	<0.001				
Gender	1.94	-0.43	4.32	0.11				
HIV	-3.07	-5.69	-0.44	0.02	-3.80	-7.03	-2.07	0.02
Diabetes	8.48	5.93	11.0	<0.001	-4.96	-17.1	-3.00	0.01
Hypertension	-8.00	-10.3	-5.72	<0.001	-7.16	-15.3	-3.21	<0.001
Renal artery stenosis	-8.39	-33.5	16.8	0.51				
Obstructive uropathy	-6.61	-16.2	2.94	0.18				
Interstitial nephritis	-12.4	-37.5	12.7	0.33				
Polycystic kidney disease	-4.91	-17.5	7.71	0.45	-13.6	-19.2	-6.30	0.04
Glomerulonephritis	-5.09	-9.01	-1.17	0.01				
Increased echogenicity	-12.6	-15.1	-10.1	<0.001	-9.29	-13.8	-4.77	<0.001
LCMD	-10.5	-12.9	-8.05	<0.001				
Length: right kidney	1.32	1.11	1.86	<0.001	5.02	3.44	6.60	0.04
Length: left kidney	1.24	1.15	1.76	<0.001	5.11	3.56	6.66	0.04

b.

	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*P*
		Lower	Upper			Lower	Upper	
Age	0.01	0.00	0.03	0.08				
Race	0.16	-0.06	0.39	0.16				
Gender	-0.21	-0.61	0.20	0.31				
HIV	-0.06	-0.51	.038	0.78	0.58	0.21	0.89	0.02
Diabetes	1.40	1.27	1.83	<0.001	0.71	0.40	0.88	.004
Hypertension	-1.25	-1.64	-0.87	<0.001	-0.90	-1.70	-0.20	<0.001
Renal artery stenosis	-1.99	-6.25	2.27	0.36				
Obstructive uropathy	5.11	3.56	6.66	<0.001	6.13	3.55	9.10	<0.001
Interstitial nephritis	-2.59	-6.85	1.66	0.23				
Polycystic kidney disease	9.98	8.05	11.9	<0.001	10.7	2.21	15.2	<0.001
Glomerulonephritis	-0.07	-0.74	0.60	0.83	2.08	1.99	2.98	<0.001
Inereased Echogenicity	-1.87	-2.30	-1.44	<0.001	-0.44	-1.11	0.17	0.02
LCMD	-1.70	-2.11	-1.29	<0.001	-0.85	-1.45	-0.25	0.01
eGFR (MDRD)	3.80	1.09	6.05	<.001	4.22	1.21	13.3	0.02

c.

	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*p*
		Lower	Upper			Lower	Upper	
Age	0.01	-0.00	0.03	0.13				
Race	0.16	-0.07	0.39	0.18				
Gender	-0.30	-0.71	0.11	0.15				
HIV	-0.06	-0.52	0.39	0.79	0.53	0.02	0.64	0.04
Diabetes	1.44	1.22	1.87	<0.001	0.63	0.32	0.85	<0.001
Hypertension	-1.26	-1.66	-0.87	<0.001	-0.92	-1.39	-0.45	<0.001
Renal artery stenosis	-0.001	-4.33	4.33	1.00				
Obstructive uropathy	5.02	3.44	6.60	<0.001	6.00	4.78	7.22	<0.001
Interstitial nephritis	-3.20	-7.53	1.11	0.15				
Polycystic kidney disease	9.73	7.76	11.7	<0.001	10.5	8.87	12.1	<0.001
Glomerulonephritis	-0.13	-0.81	0.55	0.70	3.01	1.97	5.55	<0.001
Increased Echogenicity	-1.79	-2.23	-1.35	<0.001	-0.47	-1.14	0.20	0.02
LCMD	-1.60	-2.03	-1.18	<0.001	-0.70	-1.33	-0.07	0.03
eGFR (MDRD)	3.04	2.02	5.35	<0.001	4.00	3.02	15.1	0.03

Table 3 Univariate and multivariate regression analysis (controlled for age, race and gender) with *a.* eGFR (MDRD) *b.* Right renal length *c.* Left renal length as dependent variables

LCMD Loss of corticomedullary differentiation, eGFR Estimated glomerular filtration rate, MDRD Modification of Diet in Renal Disease Study equation

Loss of CMD [284.4 OR; 95% CI (105.9 – 764.0); p <0.001] predisposed to an increased echogenic pattern. Conversely, a longer RL [0.65 OR; 95% (CI 0.57 – 0.73); p <0.001] and higher eGFR values [0.93 OR; 95% CI (0.91 – 0.95); p <0.001] were noted to be protective against the development of echogenic kidneys (Table 4a). Loss of CMD was positively influenced by IE [284.4 OR; 95% CI (105.9 – 764.0); p <0.001] and negatively influenced by longer RLs [0.67 OR; 95% CI (0.60 – 0.75); p <0.001] and higher eGFR [0.94 OR; 95% CI (0.92 – 0.96); p <0.001] (Table 4b).

a.

	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*p*
		Lower	Upper			Lower	Upper	
Age	0.95	0.93	0.96	<0.001				
Race	0.54	0.43	0.68	<0.001				
Gender	1.09	0.71	1.67	0.70				
HIV	62.8	8.67	455.7	<0.001	2.31	1.17	3.15	0.02
Diabetes Mellitus	0.06	0.04	0.11	<0.001	0.14	0.03	0.73	0.02
Hypertension	3.06	1.97	4.76	<0.001				
Obstructive uropathy	1.98	0.24	16.6	0.53				
Polycystic kidney disease	0.32	0.05	2.31	0.26				
Glomerulonephritis	1.87	0.81	4.31	0.14	0.20	0.04	0.67	0.03
LCMD	284.4	105.9	764.0	<0.001	150.1	44.9	499.2	<0.001
Length: right kidney	0.65	0.57	0.73	<0.001	0.83	0.51	0.90	<0.001
Length: left kidney	0.67	0.59	0.75	<0.001	0.87	0.49	0.91	<0.001
eGFR (MDRD)	0.93	0.91	0.95	<0.001	0.94	0.90	0.98	0.01

b.

	Univariate				Multivariate			
	OR	95% CI		*p*	OR	95% CI		*p*
		Lower	Upper			Lower	Upper	
Age	0.96	0.94	0.97	<0.001				
Race	0.54	0.43	0.67	<0.001				
Gender	1.07	0.71	1.61	0.74				
HIV	80.6	11.1	583.9	<0.001	101.7	90.0	110.1	<0.001
Diabetes Mellitus	0.07	0.05	0.12	<0.001				
Hypertension	2.54	1.67	3.83	<0.001				
Obstructive uropathy	2.45	0.29	20.5	0.41	70.3	59.2	77.3	0.04
Polycystic kidney disease	0.40	0.06	2.87	0.36	115.5	107.1	129.2	0.03
Glomerulonephritis	2.35	1.02	5.42	0.04	5.97	3.12	14.1	0.04
Length: right kidney (cm)	0.67	0.60	0.75	<0.001				
Length: left kidney (cm)	0.69	0.62	0.78	<0.001				
Increased echogenicity	284.4	105.9	764.0	<0.001	151.8	44.7	513.4	<0.001
eGFR (MDRD)	0.94	0.92	0.96	<0.001				

Table 4 Univariate and multivariate regression analysis (controlled for age, race and gender) with *a.* increased echogenicity *b.* corticomedullary differentiation as dependent variables

LCMD Loss of corticomedullary differentiation, eGFR Estimated glomerular filtration rate, MDRD Modification of Diet in Renal Disease Study equation

Figure 10 illustrates the influence of CKD risk factors on the development and prevention of renal US morphological abnormalities and changes in eGFR. HIV was noted to pose a significant risk to all four of the studied parameters, of which, its influence on the development of an echogenic pattern [2.31 OR; 95% CI (1.17 - 3.15); p 0.02] and LCMD [101.7 OR; 95% CI (90.0 – 110.1); p <0.001] was most prominent. Amongst all the risk factors PKD posed the greatest risk towards lower eGFR values [-13.6 OR; 95% CI (-19.2 - 6.30); p 0.04], longer RLs [10.7 OR; 95% CI (2.21 – 15.2); p <0.001] and LCMD [115.5 OR; 95% CI (107.1 - 129.2); p 0.03]. Hypertension was the leading independent risk factor for shorter RLs [-0.90 OR; 95% CI (-1.70 - -0.20); p <0.001].

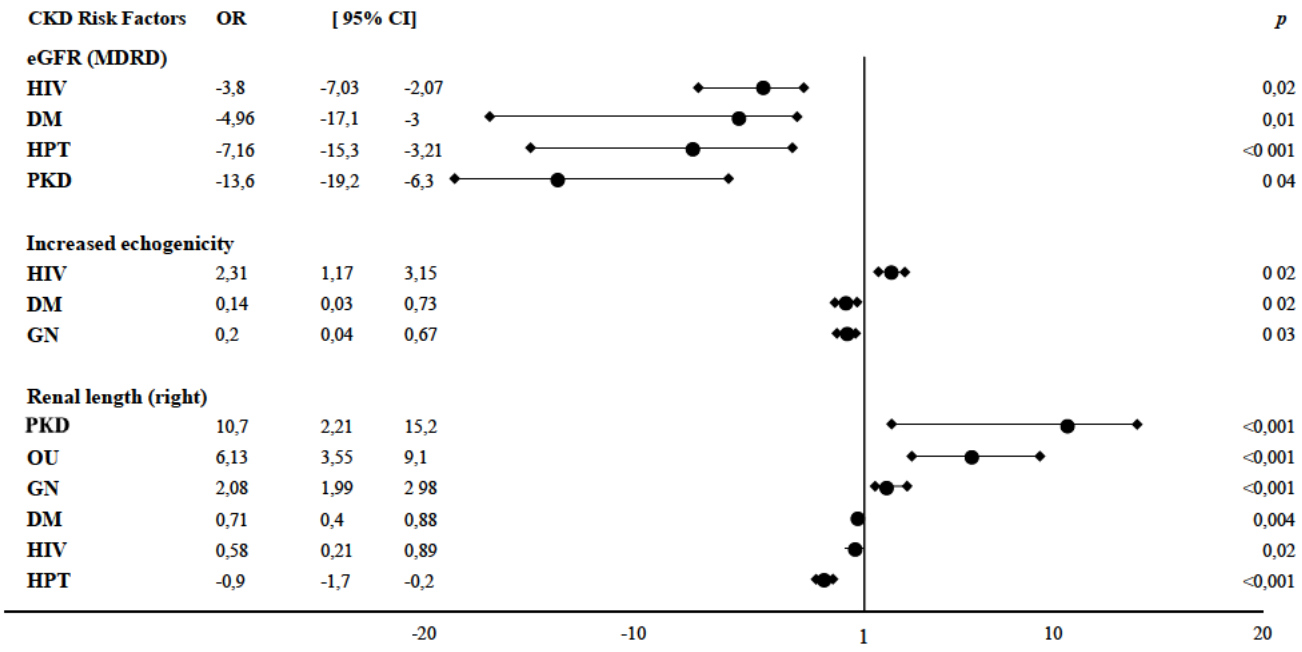

Figure 10 Forrest plot illustrating the significant risk applied upon renal function (eGFR (MDRD)) and sonographic parameters (increased echogenicity, renal length and loss of corticomedullary differentiation) by the various chronic kidney disease risk factors.
HIV Human Immunodeficiency Virus, DM Diabetes Mellitus, HPT Hypertension, OU Obstructive uropathy, PKD Polycystic kidney disease, GN glomerulonephritis

Chapter 5: Discussion of results

Accompanying CKD are deleterious structural changes to all three compartments of the kidney, viz. progressive nephron loss with parenchymal fibrosis and tubular dysfunction. Parallel to these aberrations is the deterioration of renal function at rates which are dependent on underlying genetic and environmental factors.[12,13] The end product is the mishandling of metabolites, electrolytes and urea which is coupled with a significant cardiovascular risk. The World Health Organization has elevated CKD to the 12th leading cause of death in the world in 2016. Alarmingly, by 2030 it is estimated that more than 70% of patients with ESRD will come from disadvantaged low-income regions[14].

The health care landscape in South Africa is fast evolving with the double burden of communicable (CD) and non-communicable diseases (NCD) which is fast propelling the CKD epidemic. The demands encroached by CKD upon the health care system and economy may soon become insurmountable. Compounding this epidemic further is a lack of resources, availability of RRT and specialist nephrologists (2.3 per million population).[15]

Innovative and effective strategies have been adopted to curb the impact of CKD. These approaches include increasing public awareness, early initiation of therapy at primary levels of care and prompt referral to specialist centers in the face of established CKD.[16] Despite these active measures taken to circumvent these problems, Africa still lags behind most Northern territories. Fortunately, the assessment of the eGFR and renal morphology via US are minimally invasive and cost-effective diagnostic methods of evaluating CKD. eGFR provides an estimation of renal function which portends to overall prognosis[17]. If resulted as abnormal and/or accompanied by other clinical anomalies i.e., proteinuria, renal US is utilized to delineate the anatomy of the kidney. Regrettably, US is not always readily available as skilled technicians or US machines may be scarce in resource limited settings.[18]

To our knowledge this is the first study in Sub-Saharan Africa that examines the complex and dynamic relationship between renal function (eGFR) and renal morphology on US in CKD. Both aforementioned variables are dynamic measures that may independently predict CKD, determine severity and infer risk or protection against each other. The epidemiology of CKD is also explored in this study.

The centralization of specialist services like adult nephrology and hypertension at IALCH makes this center highly representative of CKD within the province which caters to more than 10 provincial districts and 50 municipalities (Figure 11). The overall prevalence of CKD at IALCH was 9.2%. However, we acknowledge that this may be a gross underestimation of the true burden of CKD within the province as specialist nephrology services remain largely inaccessible to inhabitants of rural areas. Secondly, patients either succumb to their illness or are excluded from the national chronic renal programme prior to review by a nephrologist. Lastly, there remains no standardized eGFR formulae

which have been validated for the South African populous. The net summation of these deficiencies has left CKD poorly understood, underrecognized and the afflicted underserved.

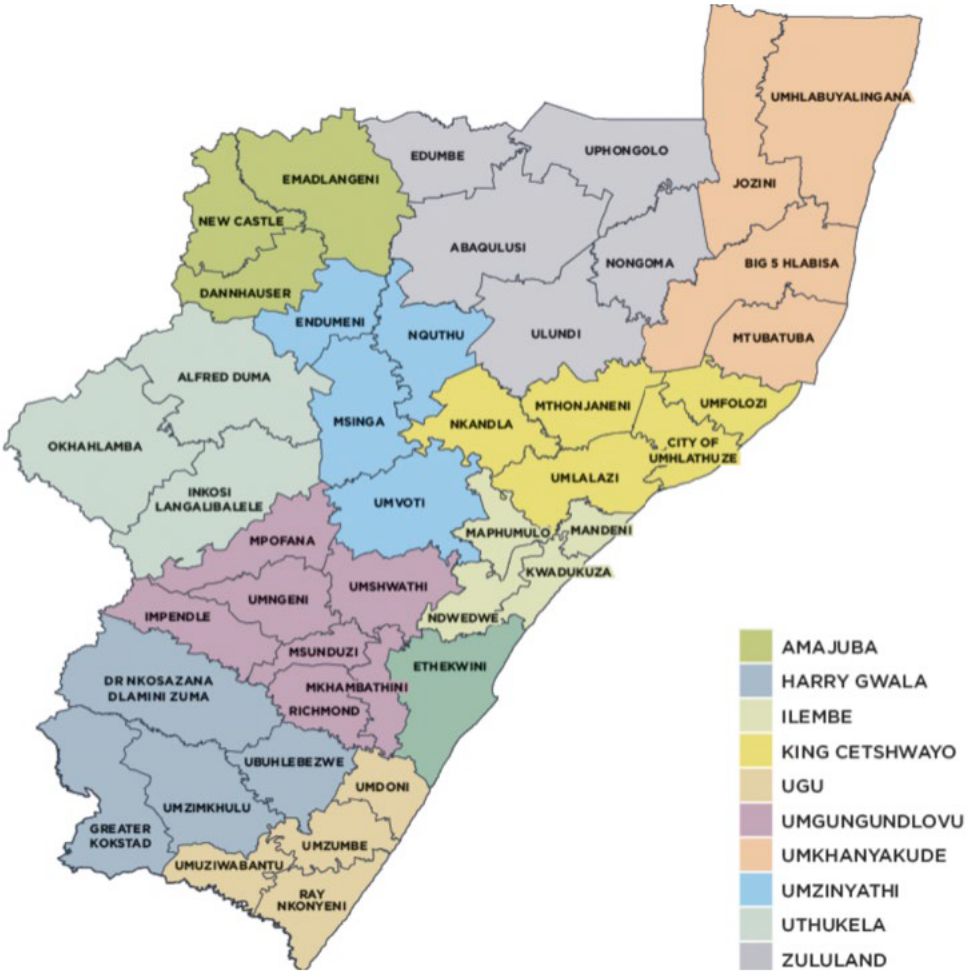

Figure 11 Geographical map of Kwa-Zulu Natal (KZN) consisting of 10 districts and 50 municipalities
https://municipalities.co.za/provinces/view/4/kwazulu-natal

Two recent meta-analyses reviewing the burden of CKD on the continent and Sub-Saharan Africa estimate rates of 3%-16.5% and 13.9% respectively. Unfortunately, at current, few high-quality studies assessing the epidemiology of CKD in South Africa has been published. This poses major consequences towards the funding of nephrology services in the country especially pertaining to the provision of RRT as the true need is not known. [19]

This study is almost exclusively made up of patients with advanced CKD (*n.* 455). Stages 3 to 5 constitute 99.1% of the sample with the greatest number of patients presenting with ESRD/stage 5 CKD (67.5%) (p <0.001). The median RLs of the right and left kidney were 8.49 ± 2.16cm and 8.60 ± 2.20cm respectively which corresponded with a low median eGFR (MDRD) of 14.4 ± 12.8ml/min/1.73m^2. It is of great concern that the sample had consisted principally of patients with advanced disease. This may allude to an accelerated progression of disease amongst Sub-Saharan Africans on the background of an increased prevalence of CD and NCDs within the province.[20,21] Though missed diagnosis or late referrals when in extremis are likely possibilities.

The mean age of patients in our study was 45.8 ± 14.3 years. Black Africans and females constituted 75.2% (*n.* 342) and 56.9% (*n.* 259) of the total sample respectively (p <0.001). This was not dissimilar to the mid-2016 population count in which Black Africans constituted 87% (*n.* 9 625 934) and females 52.1% (*n.* 5 015 112) of the total population in KZN (p= 013 ; p=0.20).[22] Overall, females were noted to have significantly lower eGFRs and RLs when compared to their male counterparts (p= 0.01).

Two studies reviewing the clinical characteristics of patients with CKD in rural and urban KZN closely mirrored the demographics of the patients represented in this study. Madala et al. studied a total of 302 patients with CKD and reported a mean age of 47.1 ± 17 years with 44% of the total sample belonging to the ESRD group.[23] Whilst, Singh et al. had reported a discrepant median age of 40.6 ± 15.2 years and 53.4 ± 14.5 years for rural and urban patients respectively. Rural dwellers had significantly lower eGFRs (16.3 ± 13.4ml/min/1.73m^2) when compared to urban residents with CKD (25.4 ± 15.9ml/min/1.73m^2) (p <0.001).[24] Both studies had a preponderance of females and Black African patients.

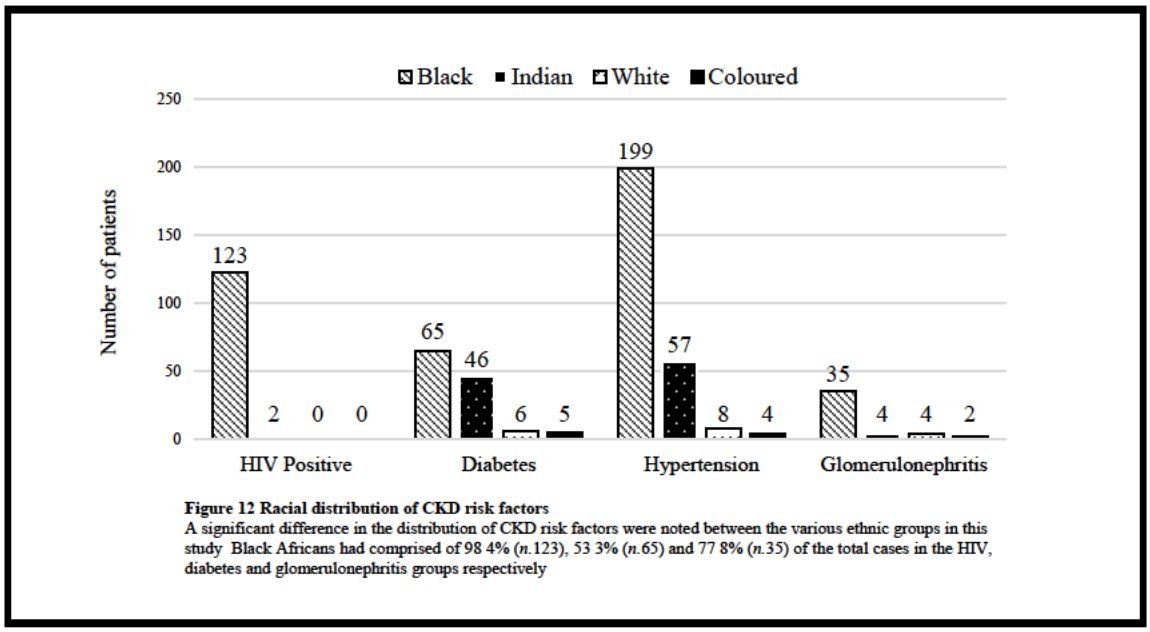

Figure 12 Racial distribution of CKD risk factors
A significant difference in the distribution of CKD risk factors were noted between the various ethnic groups in this study Black Africans had comprised of 98 4% (*n.*123), 53 3% (*n.*65) and 77 8% (*n.*35) of the total cases in the HIV, diabetes and glomerulonephritis groups respectively

A significant difference in kidney size, presence of US abnormalities and distribution of CKD risk factors were noted between the various ethnic groups in this study. Black Africans had comprised of 98.4% (*n.*123), 53.3% (*n.*65) and 77.8% (*n.*35) of the total cases in the HIV, diabetes and glomerulonephritis groups respectively. Black Africans were also found to have shorter renal lengths (right 8.40 ± 2.20cm; left 8.52 ± 2.27cm) and a lower median eGFR of 12.6 ± 11.7ml/min/1.73m2 in comparison to the other ethnic groups (Figure 12).

CKD has a strong age, racial and probably gender predilection. Normally the ageing kidney is accompanied by a concomitant loss of nephrons and thus a reduction in glomerular filtration.[25] This expected deterioration in the GFR is further compounded by the deleterious effects of other coexisting comorbidities. In Africa and other underdeveloped countries, CKD affects predominantly patients aged 20-50 years where infections like HIV and tuberculosis are common[26]. This is unlike developed countries where CKD presents in mostly middle-aged and elderly patients and is primarily caused by DM and HPT.[27] We report similar rates of HPT across all age groups. This is understandable as secondary hypertension is a product of advanced renal disease, which comprised of more than 60% of the total cases in this study.

African ancestry poses a substantial risk for the development of renal disease with a particular accelerated course. Putative polymorphisms in myosin heavy chain 9 (MYH9) and apolipoprotein L1 (APOL1) are important risk factor of FSGS, diabetic nephropathy and hypertensive nephrosclerosis.[28] The APOL1 polymorphism is said to have originated in Africa 5000 years ago in regions where Trypanosoma brucei infection (African sleeping sickness) is endemic.[29] A prevalence of 49% was reported amongst dialysis dependent Western Africans in Nigeria.[30] Interestingly, this founder effect is noted amongst Africans disseminated across the Trans-Atlantic slave trade route i.e., South and North America.[31]

Despite racial mixing individuals identified with either homozygous or heterozygous APOL1 alleles are at a considerably greater risk for the development of significant proteinuria and lower GFRs.[32] Certainly, disease expression is hastened in the presence of various environmental stressors such as HIV, DM and HPT.[33] Brazilians of West African descent were found to have a 10-fold increase in dialysis dependent CKD than their Caucasian counterparts. Allograft dysfunction and rejection was also problematic in this population.[34] APOL1 polymorphisms has also been recognized amongst individuals of Pakistani decent but found to be rare amongst Caucasians.[35]

The South African Medical Research Council reviewed disease trends and mortality rates in South Africa over a 14-year period from 1997 to 2010. DM, HPT, cerebrovascular disease and renal disease were identified as newly emergent epidemics afflicting Black Africans. Possible explanations for this

phenomenon include rapid urbanization, obesity and the adoption of a sedentary lifestyle. A similar, but less pronounced disease profile was observed in our study amongst the Indian and White patients.[36]

The 2017 South African renal registry reviewed and summarized data of patients with ESRD and/or on RRT. Hypertensive renal disease (35.1%), diabetic nephropathy (15.3%) and glomerular disease (10.3%) were the three most commonly reported primary causes of CKD.[26] Disease trends were similar in our study. KZN is the epicenter of the HIV epidemic with up to 27% of the population infected.[37] Distressingly, females and patients aged 15-49 years are disproportionately affected.[38] We report a corresponding high prevalence in HIV of 27.5% of which 63.2% were female. Systematic reviews assessing the prevalence of HIV nephropathy in South Africa report rates ranging from 21-50%.[7,23,24,26,39]

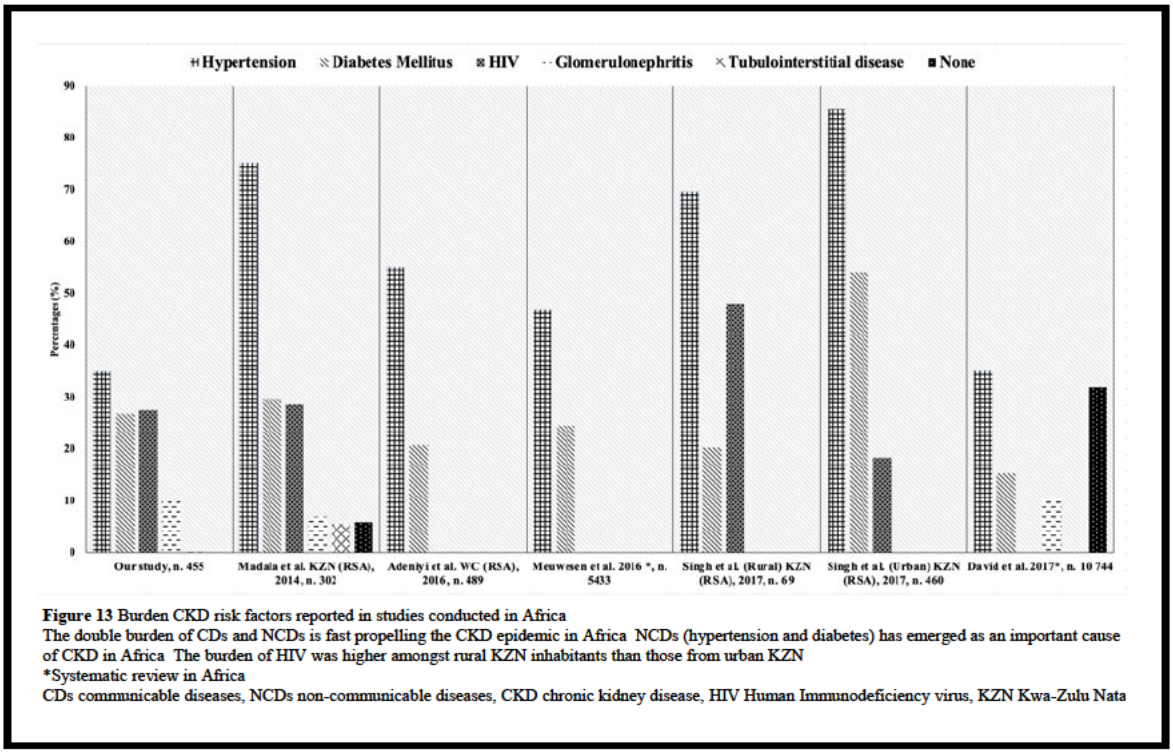

Figure 13 Burden CKD risk factors reported in studies conducted in Africa
The double burden of CDs and NCDs is fast propelling the CKD epidemic in Africa NCDs (hypertension and diabetes) has emerged as an important cause of CKD in Africa The burden of HIV was higher amongst rural KZN inhabitants than those from urban KZN
*Systematic review in Africa
CDs communicable diseases, NCDs non-communicable diseases, CKD chronic kidney disease, HIV Human Immunodeficiency virus, KZN Kwa-Zulu Nata

Figure 12 is a comparison of reported rates of CKD risk factors from 5 studies conducted in Sub-Saharan Africa. Lack of preventative strategies, late identification of risk factors and initiation of appropriate therapies have hastened NCDs into prominence as major risk factors for CKD.[40]

Completion of nephrogenesis occurs at the 36th week of gestation. Thereafter renal growth is a consequence of nephron hyperplasia rather than a further increase in nephron count.[41] A biphasic growth pattern has been described as renal size increases until the 3rd to 4th decade of life which is then proceeded by subsequent nephron loss and shrinkage.[42] The latter may occur sooner when confronted with chronic comorbidities that may accelerate glomerulosclerosis and tubular dysfunction.[43]

A change in a single sonographic parameter may initiate or accelerate the development of another renal morphological abnormality.[44] We found that kidneys noted to have both an echogenic pattern and LCMD were significantly shorter with lower eGFRs than those with only one or no observed abnormality. Alterations in intraglomerular pressure and cellular function herald disastrous renal architectural changes. This knock off effect is cumulative over time.[45]

Studies have explored the association between renal morphological parameters and function with varying results. Hoi et al. had demonstrated the strong predictive ability of cortical thickness in determining renal function, whilst other studies advocated for adjusted kidney volume or parenchymal thickness.[46] However, the use of these parameters in determining renal function continues to remain in contention. The ellipsoid formula which is used when calculating kidney volume on US may be inappropriate as the kidney is not ellipsoid in shape. Also, the landmark at which thickness (cortex or medulla) is determined has been debated.[47]

(Figure 9) We found significant associations between the changes in eGFR and the presence of abnormalities on US ($p < 0.001$). An increased echogenic pattern and alterations in RL may be considered as independent surrogate markers of renal function in CKD. IE and changes in RL are static parameters and should be interpreted with caution. RL has been shown to correlate with height, weight and BMI. Therefore, anthropometric adjustment of US indices should be performed to avoid the under or overdiagnosis of CKD. If abnormalities are considered to be severe or are accompanied by changes in eGFR or protein handling, an adjustment could possibly be overlooked.[7]

Echogenicity which describes the severity of renal sclerosis is readily determined when compared to the echo pattern of the neighbouring liver.[18] We confirmed that an increased echogenic pattern was the most significant independent predictor of renal function (MDRD) [-9.29 OR; 95% CI (-13.8 - -4.77); $p < 0.001$] in this study. Similar results were reported by Singh et al.[38] Moghazi et al. had demonstrated that IE was strongly associated with aberrations in renal histology (glomerular sclerosis, tubular atrophy, interstitial fibrosis and inflammation).[48]

Longer RLs and higher values of eGFR were noted to be protective against IE ($p = 0.01$ and $p < 0.001$ respectively). An opposite and very significant effect was seen in the presence of a loss in CMD. It was apparent from our study that longer RLs portended to the structural integrity of the kidney and is positively influenced by a higher eGFR ($p = 0.02$). The significant relationship between the reduction in RL and renal function was also established by Ahmed et al. when he concluded that RL should be used as a marker of renal function.[49]

(Figure 10) We found that HIV positivity was the most consistent CKD risk factor to significantly affect all measures of renal function with varying degrees of severity. HIV was also the only aetiology that was predictive of IE ($p = 0.02$). Cletus et al. had found that HIVAN may be diagnosed or excluded on US. He reported that a LCMD on the background of a grade 3 echogenic pattern on US was highly predictive of HIVAN. Similarly, low $CD4^+$ counts and the ensuing immunosuppression encountered in uncontrolled HIV infection was highly predictive for the development of an increased echo pattern.[50] Renal size in HIVAN is variable with some studies reporting wider and thicker kidneys.[51]

Diabetes was found to be protective against an IE pattern but like hypertension was shown to be a significant independent risk factor for both lower eGFR values and shorter RL.[52] Hyperfiltration and longer kidneys are hallmarks of early diabetic nephropathy. However, like in hypertensive kidney disease, small kidneys are seen in late disease due to unabated glomerular sclerosis and fibrosis.[53,54]

Chapter 6

Study limitations

Limitations are expected by virtue of a retrospective study design. An analysis of the temporal change in the significance of associations and CKD risk factors was not possible. The study also may have been subject to sampling bias. Patients with ESRD predominated the sample over patients with less advanced disease. Referral of those in need of urgent RRT are prioritized. Anthropometric measurements i.e., weight, height and body mass index has been reported in previous studies and correlated with renal US parameters and function. Unfortunately, the anthropometric data of many patients were not available. We recognize that weight and height adjusted length may have produced dissimilar correlates. However, this effect may have been minor in the setting of advanced or end-stage disease.

No cases reported the grade of renal echogenicity, width and volume. Consequently, further correlations could not be investigated. Of particular interest would be the development of predictive models between US indices and renal function e.g., echogenic grade and eGFR. Lastly, CKD-EPI has been reported to be the most superior equation and should be preferentially used to assess disease burden. Nonetheless, recent studies have found the performance of MDRD to be comparable to CKD-EPI in both the early and late stages of CKD amongst Africans.[23]

Chapter 6

Summary and Recommendations

Sonographic measures are significant predictors of renal function. This study revealed that changes in RL and the presence of an increased echogenic pattern indicate irreversible damage and is highly predictive of renal dysfunction. This may predate or be accompanied by a fall in eGFR. The need for the double determination of renal function to diagnose CKD may become obsolete with the development of predictive 'best fit' models which would match a specific change in morphology (echogenic grades) to a particular CKD stage. Due to the strong predictive association between HIV seropositivity and the development of echogenic kidneys, the use of US in HIV prevalent populations would be an invaluable method of screening for CKD.

This study also adds further insight into the epidemiology of CKD in South Africa, which is certainly sparse and incomplete. As demonstrated within this cohort, disease prevalence was advanced and accelerated. Undoubtedly, the duality of both CD and NCDs is bound to worsen the burden of CKD locally. Therefore, primary preventative measures and the treatment of associated risk factors should be addressed earlier in high-risk populations. The ethnic and gender discrepancies reported in this study are alarming. Black Africans and females are at a significant risk of morbidity and mortality from CKD. Thus, further studies in Africa exploring the interaction between genetic and environmental stressors in CKD are essential.

Chapter 6

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Chapter 6

Appendices

1. Data collection sheet
2. Biomedical and Research Ethics Committee: letter of approval
3. Site approval: letter of approval to conduct research
4. Kwa-Zulu Natal Department of Health: letter of approval to conduct research

Appendix 1: Data collection Sheet

ADMINISTRATIVE DATA		DEMOGRAPHICS			AETIOLOGY				RENAL US MORPHOLOGY					RENAL FUNCTION
STUDY NO.	Hospital no.	Age	Race	Gender	HIV	Diabetes	Hypertension	Other risk factors	Length: right (cm)	Length: left (cm)	Echogenicity	Corticomedullary differentiation	Other findings	eGFR (MDRD)

Appendix 2: Biomedical and Research Ethics Committee: letter of approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

HRKM Ref: 334/17
NHRD Ref: KZ_201708_003

Date: 24 August 2017
Dear Dr AG Frank
UKZN

Approval of research

1. The research proposal titled **'The correlation between renal sonography and renal function in chronic kidney disease at Inkosi Albert Luthuli Chief Hospital. A retrospective descriptive study'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

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

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 18/09/17

Appendix 3: Site approval: Letter of approval to conduct research

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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www.kznhealth.gov.za

DIRECTORATE:
Office of The Medical Manager
IALCH

Reference: BE017/17
Enquiries: Medical Management

18 July 2017

Dr A G Frank
Discipline of Medicine
IALCH

Dear Dr Frank

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **The correlation between renal sonography and renal function in chronic kidney disease at Inkosi Albert Luthuli Central Hospital.**

Kindly take note of the following information before you continue:

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

Yours faithfully

[redacted]
.....
Dr L P Mtshali
Medical Manager

Fighting Disease, Fighting Poverty, Giving Hope

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Details of any financial or human resource implications to KEH, including all laboratory tests, EEGs, X-rays, use of nurses, etc. (See Addendum 1)
5. Declaration of all funding applications / grants, please supply substantiating documentation.
6. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** at the Biomedical Research Ethics Administration, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
IALCH

Investigator/s:
Principal: DR A.G. Frank
Co-investigator: Prof Assoungo
Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager:
[redacted]
Date: 19/07/2017

Site 2 address:

Investigator/s
Principal: _____
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:

Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

Appendix 4: Kwa-Zulu Natal Department of Health: letter of approval to conduct research

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

DIRECTORATE:
Office of The Medical Manager
IALCH

18 July 2017

Dr A G Frank
Discipline of Medicine
School of Clinical Medicine

Dear Dr Frank

Re: Approved Research: Ref No: BE017/17: The correlation between renal sonography and renal function in chronic kidney disease at Inkosi Albert Luthuli Central Hospital.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

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