



**A DESCRIPTIVE STUDY OF CHRONIC KIDNEY DISEASE
(STAGES 3-5) IN CHILDREN AT CHRIS HANI
BARAGWANATH ACADEMIC HOSPITAL, 2000-2019**

by

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DECLARATION

Declaration: Student's contribution to article(s) and agreement of co-author(s)

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DEDICATION

This dissertation is dedicated to God without Him this would not have been possible; my family for their constant love and support in my journey and to all the children with chronic kidney disease (CKD).

ABSTRACT

Background

The epidemiology and outcome of chronic kidney disease (CKD) in children of less resourced countries are largely underreported because of paucity of data systems.

Methods

A retrospective follow-up study of children aged 2 to 14 years with CKD stage 3 to 5 at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa, from 2000-2019.

Results

A total of 198 children were analysed. Sixty-five (32.8%), 47 (23.7%), and 86 (43.4%) had CKD stages 3, 4 and 5 at diagnosis, respectively. The median (inter quartile range (IQR)) age at diagnosis was 7 (4-11) years and duration of follow up was 1.2 (0.3-3.2) years. The calculated annual incidence in 2001 to 2019 ranged from 9.3 to 29.7 per million age related population (PMARP). Glomerular disease accounted for 74 (37%); congenital anomalies of the kidney and urinary tract (CAKUT) for 64 (32%).

At final outcome, 108 children had CKD stage 5. Seventy-three (67.5%) received kidney replacement therapy (KRT) and 35 (32.4%) treated conservatively. The mean rate of decline in eGFR from baseline to final visit was 4.90 (SD 7.03) ml/min/BSA per year. The mortality rate was 9.8 (95%CI:7.3 to 13.1) person-years (PY), contributed by 46 (23.3%) children. The two-year survival for glomerular disease was 50% compared to 90% for CAKUT. Risk of mortality increased in CKD stage 5 (AHR=3.5; 95%CI:1.5-7.9, p-value 0.002), hypoalbuminemia (AHR=2.6; 95%CI:1.0-6.2, p-value 0.030) and glomerular disease (AHR=2.5;95%CI:1.0-6.3, p-value 0.046).

Conclusion

This cohort presented in advanced CKD. Barriers to access renal services should be addressed to achieve sustainable developmental goals (SDG).

Keywords: Chronic kidney disease, low- and middle-income countries, Sustainable developmental goals, kidney replacement therapy, non-communicable disease, conservative

kidney management, Incidence per million age-related population, Children, South Africa, Glomerular disease.

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NOMECLATURE

AKI:	Acute Kidney Injury
CAKUT:	Congenital Anomalies of the Kidney and Urinary Tract
CKD:	Chronic Kidney Disease
CRRT:	Continuous Renal Replacement Therapy
ESKD:	End Stage Kidney Disease
HD:	Haemodialysis
HIC:	High Income Countries
KRT:	Kidney Replacement Therapy
LMIC:	Low- and Middle-Income Countries
PD:	Peritoneal Dialysis
PMARP:	Per Million Age-Related Population

CHAPTER ONE – INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

Chronic kidney disease (CKD) is one of the silent causes of mortality in the adult and paediatric populations. It is said to become the 5th leading cause of mortality by year 2040 (1). There is no clear data on incidence of CKD in South Africa (SA). This is addressed in the sustainable developmental goals (SDG) (2). With the decreasing number of kidney transplantations occurring in low resource settings (3), it becomes essential to report on the epidemiology, risk factors, spectrum of diseases and outcomes of children with CKD, especially moderate to severe CKD i.e., CKD stages 3 to 5.

The Kidney Disease Improving Global Outcomes (KDIGO) provides evidence-based clinical guidelines on the management of kidney diseases. It defined CKD as abnormalities of kidney structure or function that is present for greater than three months (4). Chronic kidney disease is further classified into different stages of severity based on the estimated glomerular filtration rate (eGFR) and albuminuria category (4). The most severe form of CKD is kidney failure (KF), also known as end stage kidney disease (ESKD) or CKD stage 5 (5). It is defined as an eGFR less than 15ml/min/1.73m² or the need for dialysis (5). Dialysis therapy and or kidney transplantation are forms of kidney replacement therapy (KRT) which substitute life-sustaining kidney function (6). The latest South African Renal Registry (SARR) reports on 849 patients starting KRT in the year 2021, the majority of whom (80%) were treated in the private sector. This provided an incidence of 14.1 per million population (pmp). In South Africa, 85% of the population attend the public healthcare facilities and 14.6% attend private healthcare (7).

Africa is burdened with communicable and non-communicable diseases, in addition to socio-economic challenges (1, 8). This shapes the unique patterns of aetiologies, risk factors and outcomes of children with CKD. Chronic kidney disease can be asymptomatic until it progresses to advanced stages, leading to underestimates of incidence and prevalence (9). Delayed CKD diagnosis can lead to preventable morbidity and increased health care costs (9). There is a pressing need for early identification and prevention strategies (10). Improved health care systems and adequate resource allocation for patients with CKD is proposed. (8).

More than half of the children in the world less than 15 years of age reside in less resourced countries (11). This study aimed to describe the epidemiology, demographic characteristics, aetiology and risk factors of children, 2 to 14 years, diagnosed with moderate to severe CKD over two decades; as well as analyse the complications, treatment and outcomes. This is a single centre study in a Tertiary Hospital in Soweto, South Africa, Chris Hani Baragwanath Academic Hospital (CHBAH). The hospital provides tertiary services to surrounding regions within and outside of Gauteng province.

1.2. LITERATURE REVIEW

1.2.1. DEFINITION

Kidney diseases play a significant role in the cause of morbidity and mortality worldwide, with an increasing prevalence globally (12). The global annual mortality due to chronic kidney disease (CKD) is predicted to be 2.2 million in 2040, up by 1 million from year 2017 (8). Early stages of chronic kidney disease in children are often under diagnosed and under reported as they are frequently asymptomatic (13). It is advantageous to diagnose CKD in early stages so timeous treatment can be implemented to preserve residual renal function.

Although widely adopted, the KDIGO guideline is criticized for its limited applicability. The criteria for eGFR below 60ml/min/1.73m^2 are inapplicable to children less than two years of age, since in the newborn period the eGFR is significantly less than 60ml/min/1.73m^2 , and increases rapidly reaching normal adult values by 2 years of age (4, 14). Therefore, normal maximal values for eGFR for this age group will naturally be less than those of an older child or adult (4). In addition, children born with clinically severe congenital abnormalities of the kidney and the urinary tract (CAKUT) are flagged to have CKD before awaiting three months for this diagnosis (13). It is just as important to report on CKD stages 3 to 5 in children less than 2 years of age using validated formulae for eGFR. Various formulae are available to determine eGFR; however, the modified Schwartz formula is the most widely utilised in children (13, 15, 16). This age group of children less than two years, however, did not form part of our study.

1.2.2. EPIDEMIOLOGY

There is little information on the epidemiology of chronic kidney disease in children, especially in less resourced countries (13). In high income countries such as Europe, the incidence of CKD stages 3-5 in children is 11-12 per million of the age-related population (pmarp) (13). In the United States and Canada, the incidence of kidney failure in children 0-19 years of age is 9-16 pmarp (13). Gender and race also play a pivotal role in the incidence of CKD. It is higher in males because of greater occurrence of CAKUT in this gender (13). In North America, Australia and New Zealand there is a higher incidence of CKD and kidney failure in African American and indigenous children compared to the rest of the paediatric population (13). This could be attributed to genetic predisposition and to the social determinants of health.

In Africa the incidence of CKD is mostly unknown due to scarce data systems. (17). The incidence of CKD in sub-Saharan Africa is thought to be higher than is known (18). The limited studies on childhood kidney failure in sub-Saharan Africa are primarily from Nigeria and South Africa (19). These single-centre studies report an incidence of CKD in children below age of 16 years to be 3 pmarp in Nigeria and 1-2 pmarp in South Africa (13). Reasons for the low incidence could be due to short study period, lack of national renal registries documenting all stages of CKD and missed diagnosis.

South Africa (SA) although an upper middle-income country (UMIC), has the highest Gini coefficient (0.63) globally, reflecting significant wealth disparities (20). Gauteng, a small yet most urbanised province, comprises the largest share of South Africa's population. The median age in South Africa is 27.6 years in year 2021 (21). It is challenging to perform large scale epidemiology studies in SA because of the limited renal services in some provinces. A recent adult study in a tertiary hospital in Bloemfontein report an average annual ESKD incidence of 49.9 (95 %confidence interval [CI], 35.8-64.0) per-million-population (22). A study done in Kwa-Zulu Natal, South Africa on children less than 16 years of age with CKD stages 2 to 5 identified 89 (68.2%) children with CKD stage 3 to 5 over their 11-year study period (17). In the 2022 South African Renal Registry (SARR), there were 822 adult patients who started KRT, an incidence of 13.3 per million population (pmp) (7). The SARR reports only on patients in CKD stage 5 who receives kidney replacement therapy which limits the calculation of CKD incidence. In the private health sector in SA, the number of Discovery Health Medical Scheme (DHMS) members who are registered as having CKD exponentially

increased from 2008 with 1747 members registered as having CKD to 8113 members in 2022, i.e. a 4.6-fold increase in incidence (23). This may be due to increase registration of patients with CKD by staff members. The incidence of CKD in children residing in Gauteng is currently unknown.

Although the diagnosis of CKD increases with advancing age, young adults in Sub-Saharan Africa (SSA) are highly affected due to greater incidences of chronic glomerulonephritis, alternative herbal medication, and communicable diseases (22). This is compounded by the limited number of nephrologists, especially paediatric nephrologists (24). Other contributing factors include limited resources, poor access to kidney replacement therapy, and high prevalence of poverty (24). It is proposed a national registry in SA, like the SARR, for children with CKD stage 3 to 5 be developed. It will provide vital information on the epidemiology of CKD in children in SA and help identify risk factors for progression of kidney disease (18).

1.2.3. RISK FACTORS

Besides genetic factors, low- and middle-income (LMIC) countries face the challenge of CKD enhanced by infections, prematurity and low birth weight (25). In addition, socio-economic influences such as inadequate sanitation, pollution, malnutrition and traditional medicine propel CKD (25). Another major contributor to the burden of CKD is acute kidney injury (AKI) due to hypovolemia and septic shock complications and is associated with high mortality and progression to CKD (14, 25).

Infectious diseases in LMIC contributing to a greater incidence CKD include tuberculosis, hepatitis, schistosomiasis, post-infectious glomerulonephritis and human immunodeficiency virus (HIV) associated nephropathies (18, 25). At Chris Hani Baragwanath Academic Hospital (CHBAH) between 1990 and 2012, acute post infectious glomerulonephritis was the most common cause of crescentic glomerulonephritis, a risk factor for CKD (26). In a ten-year review study at the Red Cross Children's Hospital on children with crescentic glomerulonephritis, majority (46%) of the children had APIGN as the cause. On one year follow up, 75% of all children with crescentic glomerulonephritis either developed CKD, needed chronic dialysis or a kidney transplant (27).

1.2.4. AETIOLOGY

Data from renal registries in high income countries show that in children, CAKUT predominate over glomerular disease (12). Studies from LMIC in Africa, Asia, Middle East and South American all show glomerular disease is the main cause of paediatric kidney disease, in contrast to high income countries (12). The reason for the difference is allegedly due to more exposure to immune-stimulating antigens associated with glomerulonephritis in the LMIC (18). In addition, in LMIC, the proportion of CKD due to CAKUT is determined by the availability of antenatal sonars, mortality in infancy, and the progression to kidney failure after childhood (28).

The two frequent causes of kidney failure in children of South Africa are glomerular disease (83%) followed by CAKUT (8.5%) for the year of 2012 (18). Glomerular disease occurs mainly in children older than 10 years while CAKUT predominates in younger children (13,19). The causes of glomerular disease vary among different continents in Africa, ranging from parasites like bilharzia to malaria, hepatitis B, syphilis, HIV and other infections (12, 29, 30). Focal segmental glomerular sclerosis is increasing across all racial groups in South Africa (31). It is one of the classic causes of steroid resistant nephrotic syndrome (SRNS) (31). Steroid resistant nephrotic syndrome is one of top three causes of end stage kidney disease (ESKD) in the 2006 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) on children who were transplanted (32).

There is increasing awareness of HIV-related nephropathy causing significant morbidity and mortality in children in Africa and sub-Saharan Africa (33). HIV-associated nephropathy (HIVAN) is characterised by rapid progression to kidney failure, without treatment (34). Prior to the implementation of the antiretroviral (ARV) program, the most rapid progressors died in infancy (35). Early diagnosis of HIV and immediate institution of antiretroviral therapy decreased early infant mortality by 76% and HIV progression by 75% (35). The first rollout of the HIV/AIDS program in South Africa in 2004 lead to increased testing and survival (36). The estimated proportion of child deaths due to AIDS in South Africa reached a peak of 37–39% around 2005–2006 with a sharp decline towards the end of the decade (37). There is a wide variety of renal diseases in children with HIV, these include electrolyte and tubular abnormalities, acute kidney injury, thrombotic microangiopathies as well as glomerular diseases that cause proteinuria HIVAN and HIV-associated immune complex disease kidney

disease (HIVICK). The proteinuria can range from asymptomatic moderately increased albuminuria to complete nephrotic syndrome. Some of the children can progress to CKD (33).

Of the CAKUT conditions, posterior urethral valves (PUV) are a common cause of congenital obstructive uropathy and can lead to CKD (38). At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), 44.8% of children with CAKUT had posterior urethral valves (PUV) (39). At CHBAH, 34.8% of patients with PUV present with CKD at the final follow up visit (40).

Metabolic and genetic diseases such as renal tubular acidosis, cystinosis, and oxalosis are rare diseases with high risk of progression to CKD (30). Local data for children at CHBAH with primary Hyperoxaluria and CKD reports a mortality rate of 78.9% (41).

1.2.5. COMPLICATIONS

Chronic kidney disease is a pro-inflammatory condition with multisystem effects (42). A SA study in 2017, reports modifiable cardiovascular risk factors such as increased total cholesterol and decreased albumin levels are associated with mortality (43). More aggressive treatment of blood pressure, hyperphosphatemia, acidosis and dyslipidaemia may slow the progression of CKD as well as decrease cardiovascular disease (CVD) (44). Other important complications include stunting and anaemia (44). Anaemia, defined by KDOQI as Hb concentration is <11.0 g/dl in children 0.5–5 years, <11.5 g/dl in children 5–12 years, and <12.0 g/dl in children 12-15 years, is associated with high morbidity and mortality in children with CKD (45, 46). A SA study in 2018 reports serum ferritin levels and red cell distribution width to be independent predictors of anaemia with or without iron deficiency in children with CKD (46). A study in a tertiary hospital in India identifies anaemia, hypocalcaemia, short stature and hyperparathyroidism significantly correlating with severity of CKD in children (47).

1.2.6. TREATMENT

Children with kidney failure have the following four treatment options: kidney transplantation, peritoneal dialysis (PD), haemodialysis (HD) and conservative kidney management without dialysis. In SA, UK and most other European countries PD is the first treatment of choice (48). In the 2012 SARR, the most common mode of KRT for children was peritoneal dialysis (61%) compared to haemodialysis (39%) (18). In contrast over seventy percent of adult patients in SA received HD while 18% received PD and 10.6%

received a kidney transplant in 2018 (49). Three paediatric dialysis units in Gauteng province (CHBAH, CMJAH, private hospital) treated 75% of South Africa's children in 2012 (18). Dialysis in the private sector is equivalent to the best dialysis centres in the world, however, dialysis in public sector lags due to various reasons including high costs (50).

Treatment requires skilled medical and nursing staff. Unfortunately, Africa experiences a shortage and instability of skilled healthcare workers. In addition, migration of healthcare workers to high-income countries, has a great impact on public healthcare systems and delivery, especially affecting India, Nigeria, Pakistan, and South Africa countries where most migration takes place (51). Training of allied healthcare workers such as nurses, pharmacists, and community healthcare workers, can provide a solution by taking on uncomplicated tasks (such as urinalysis) in multidisciplinary clinics, hypertension centres, and patient triage. However, for this to be effective, training modules and protocols of disease diagnosis, treatment and referral will need to be in place. (51).

Transplantation tends to be more cost effective compared to dialysis and produces better quality of life (50). For most LMIC, transplantation is limited by resources, including low numbers of registered organ donors (only 0.2% in South Africans) and survival is adversely affected by the affordability of immunosuppressive drugs, malnutrition and infectious disease (50). Sub-Saharan Africa still falls into the lowest quartile of transplantation rates worldwide (24) and in SA, transplant centres are currently limited to a few major cities (24).

There is a national KRT rationing policy in place for patients in the public sector incorporating criteria that selects patients considered to benefit the most from transplantation to balance the growing need for KRT in a resource constrained environment (22).

Conservative kidney management (CKM) is a treatment option for families who choose not to undertake KRT (51). Effective CKM and KSC (kidney supportive care) programs are needed in both high and low resource settings. Conservative kidney management and KSC are core components of integrated kidney care (52). A recent local study in Cape Town has developed a tool kit [Paediatric Feasibility Assessment for Transplantation (pFAT)], a psychosocial risk score developed in South Africa to support transparent eligibility assessment in a low-resource setting (53). It highlights the need to address specific psychosocial and socioeconomic barriers, to encourage equitable access to KRT. Equally important, is the need for strategies to delay CKD progression (53). Patient compliance to the KRT program is also important in ensuring continuity of care.

1.2.7. OUTCOME

The mortality rate in children on KRT is approximately thirtyfold greater than their healthy counterparts (13). Patients lost to follow up can be a potential confounding variable leading to underestimation of the mortality rate. The major causes are cardiovascular diseases and infections, contributing 30-40% and 20-50% of deaths respectively (13). Infection is now the commonest cause of hospital admissions compared to acute rejection for children who received a kidney transplant (13).

Chris Hani Baragwanath Academic Hospital (CHBAH) also known casually as “Bara” is the largest hospital in South Africa and Africa. It’s size (0.70 km²) and bed capacity (3200 beds and 429 buildings) places CHBAH among the top ten largest hospitals in the world (54).

The hospital is located in Soweto, Johannesburg. Chris Hani Baragwanath Academic Hospital is a teaching hospital affiliated to the University of the Witwatersrand Medical School, along with three other nearby teaching hospitals. In addition to being a tertiary referral hospital for much of Gauteng province (11.4 million), Northwest province (3.7 million), parts of the Northern Cape, and informally the rest of South Africa, except the Western Cape (54), it also provides service to its immediate population of at least 1.5 million adults and children in the surrounding Soweto (54). In Johannesburg, CHBAH is a tertiary academic referral hospital serving regions D, F, and G, see figure 1.1. It has a total of 408 paediatric beds. The Paediatric Renal Unit at CHBAH consults up to 400 inpatients and 1500 outpatient visits annually. The unit offers acute and chronic PD as well as acute HD. Patients requiring chronic HD and transplantation are referred for quaternary services at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), since June 2021 also to Nelson Mandela Children’s Hospital (NMCH). Continuous renal replacement therapy (CRRT) is offered in PICU by the Intensivists at CHBAH.

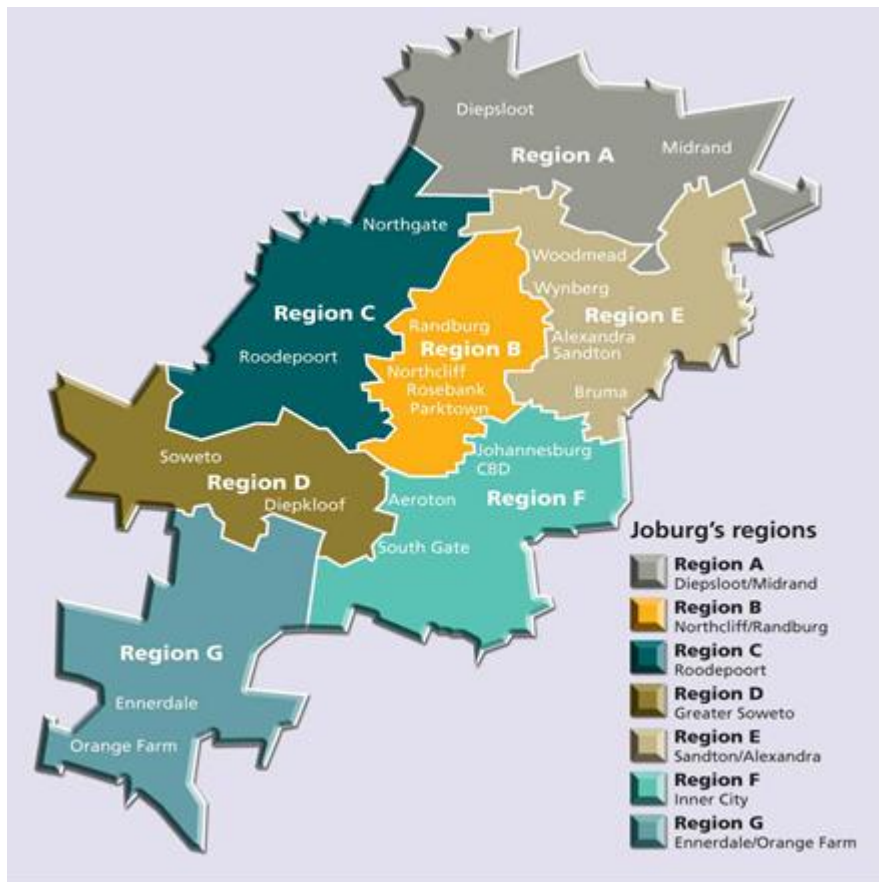


Figure 1. 1 Johannesburg regions. Available from: <https://www.commonwealthofnations.org/partner/city-of-johannesburg-metropolitan-municipality/>

This study aimed to address the research gap in the epidemiology, aetiology, risk factors, and outcomes of children with moderate to severe CKD in a SA setting.

1.3. AIMS AND OBJECTIVES

1.3.1. AIMS

This study aim was to describe the epidemiology, and characteristics of patients with an initial diagnosis of CKD stage 3 to 5 at the paediatric renal unit at CHBAH. The study also aimed to analyse the aetiology and risk factors associated with poor outcome i.e., end-stage kidney disease (ESKD) or death.

1.3.2. OBJECTIVES

- 1.3.2.1 To determine the frequency of kidney failure (CKD stage 5 or initiation of kidney replacement therapy) in children diagnosed with moderate to severe CKD at CHBAH paediatric renal unit between 01st January 2000 and 31st December 2019.
- 1.3.2.2 To describe the demographic characteristics, aetiology and risk factors of children with CKD stage 3 to 5.
- 1.3.2.3 To analyse complications, treatment and outcomes of children with CKD stage 3 to 5.

CHAPTER TWO – METHODS AND MATERIALS

2.1. STUDY DESIGN AND SITE

This was a retrospective observational study of children with CKD stage 3 to 5, treated at the Paediatric Renal Unit of Chris Hani Baragwanath Academic Hospital (CHBAH) from 01 January 2000 to 31 December 2019. Archived patient records were retrieved to identify patients.

2.2. STUDY POPULATION

The paediatric renal unit provides services to patients admitted to the neonatal unit, general paediatric wards, paediatric oncology unit, paediatric surgical disciplines including the burns unit, and the paediatric Intensive Care Unit. This study population included patients from two years to 14 years of age who consulted at the paediatric renal unit at CHBAH during the study period.

These patients were categorised into three groups based on the eGFR: CKD stage 3 (eGFR 59 – 30 mL/min/1.73m²), CKD stage 4 (eGFR 29 – 15 mL/min/1.73m²) and CKD stage 5 (eGFR less than 15 mL/min/1.73m² or initiation of dialysis) at diagnosis (4).

The following flow chart (Figure 2.1) shows how the children were sampled and included in the study:

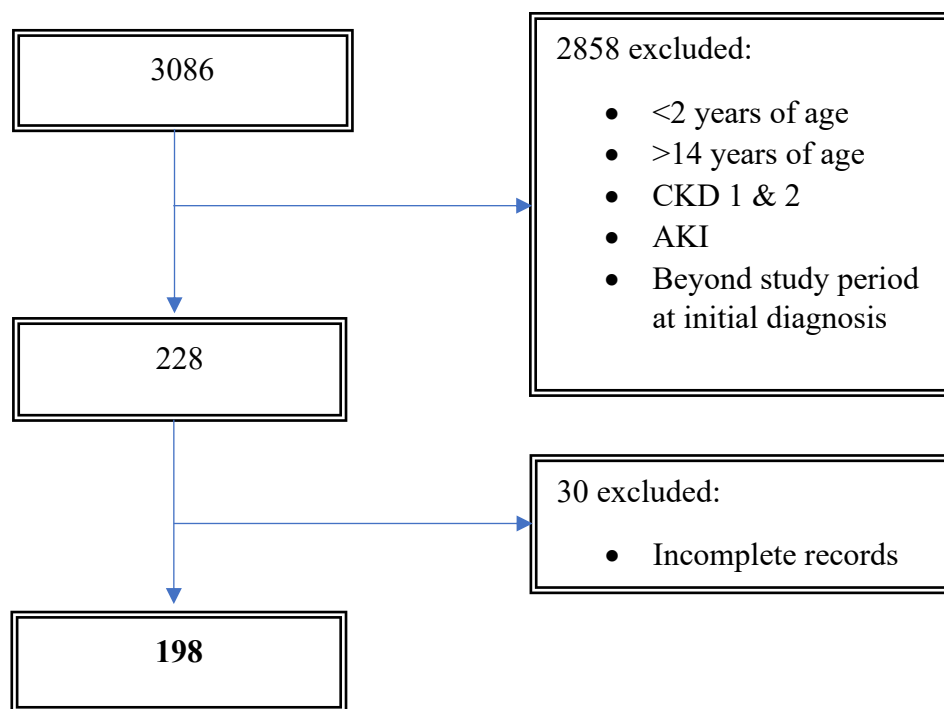


Figure 2. 1 Flow chart of inclusion criteria of the study population.

2.2.1. Data sources

Data was collected from patient clinical records stored in the renal unit. The study variables included demographics and clinical variables. Kidney function was assessed by estimation of the GFR (eGFR) using the modified Schwartz formula (16) for categorisation of CKD stages.

The aetiology was grouped into glomerular causes and non-glomerular causes. Risk factors included a family history of renal disease and neonatal factors such as prematurity, low birth weight and AKI. Complications were assessed by recording of initial consult results for presence of cardiovascular disease, anaemia, hypothyroidism, mineral and bone disease, metabolic acidosis, hypoalbuminemia and dyslipidaemia.

Management was grouped into conservative management and kidney replacement therapy. Children outcome to survival or death was recorded and analysed. Transfer out to another renal facility during the study period was counted as survivors. Patients who have not adhered to scheduled visits were recorded as lost to follow-up. Ethics permission was not obtained to prospectively follow up on the outcome of patients lost to follow up. Refer to definitions and database appendices for all the variables.

2.2.2. Outcome measurement

Outcome variables included active patient, transfer to another renal facility, lost to follow-up, or death.

Treatment variables included PD, HD, or CKM.

2.2.3. Study time

Data was collected for the 20-year period from January 2000 to December 2019. Analysis was performed from initial diagnosis of CKD stage 3, 4 or 5 to final outcome or end of the study period in December 2019, whichever came first.

2.3. DATA ANALYSIS

Data was managed using STATA version 17 (55).

Annual Incidence rates Per Million Age Related Population (PMARP) was calculated using the formula:

$$\text{New CKD 3 to 5 minus cases outside Gauteng for year} \times 1\text{million} \div \text{population indices for children aged 2 to 14 years for the same year.}$$
It was calculated for each year and reported as a range for the year 2001 to 2019.

The population indices were supplied by the District Health Information System (DHIS), which are obtained from the STATS_SA database.

Categorical variables were summarised using frequencies and percentages. Laboratory variables were categorised based on the recommended clinical threshold values for normal range. Continuous variables were assessed for normality using the Shapiro Wilk test and the histogram plots with a superimposed normal curve. Since all the variables deviated from the normal distribution, the median and interquartile range (IQR) were used as the measures of central tendency. The Kruskal Wallis test was used to test the significance difference of laboratory findings between the CKD stages. To determine the factors associated with mortality among CKD patients, the Cox proportional hazard model was used. Kaplan and Meier curves were used to describe the mortality rates between groups of categorical variables. The

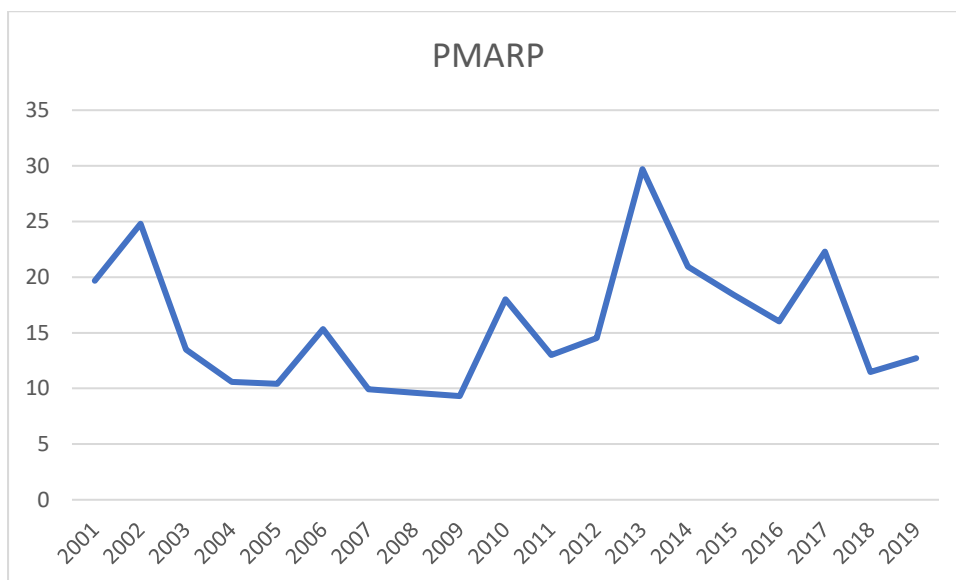
univariate and multiple Cox regression models were fitted. The proportional hazard assumption was assessed using the Scholefield residual test. Significance was set at 5%.

2.4. ETHICS

The study protocol was accepted by the University of the Witwatersrand Human Research Ethics Committee, certificate number M210468 and approved by CHBAH Paediatric department as well as the Medical Advisory Committee (MAC). The study was registered in the National Health Research Database (NHRD). The research was performed in line with the principles of the Declaration of Helsinki. Informed consent was not required due to the study being retrospective. Each patient had a study number to ensure anonymity.

CHAPTER THREE – RESULTS

A total of 65 (32.8%), 47 (23.7%), and 86 (43.4%) patients had CKD stages 3, 4 and 5 respectively. The calculated incidence for 2001 to 2019 ranged from 9.3 to 29.7 PMARP as seen in figure 3.1.



*The denominator for year 2000 could not be supplied by DHIS.

Figure 3. 1 PMARP per year

3.1. BASELINE CHARACTERISTICS AT DIAGNOSIS

Table 3.1 shows the baseline characteristics of the participants at diagnosis. The overall median (IQR) age at initial diagnosis of CKD stage 3 to 5 was 7 (4-11) years. Of the 41 (20.7%) who resided outside Gauteng Province, 21 (51.2%) presented in CKD stage 5, compared to 65 of 157 (41.4%) who resided in Gauteng.

Table 3. 1 Baseline characteristics at diagnosis

	CKD stage 3 <i>n</i> = 65 (32.8%)	CKD stage 4 <i>n</i> = 47 (23.7%)	CKD stage 5 <i>n</i> = 86 (43.4%)	Total <i>n</i> =198
Age (years) Median (IQR)	7 (4 -10)	6 (3 -10)	7 (5 -11)	7 (4-11)
Weight (z-score) Median (IQR)	-1.3 (-3.0 to 0.4)	-1.8 (-2.7 to -1.0)	-1.6 (-2.9 to -0.4)	-1.6 (-2.8 to -0.4)
Height (z-score) Median (IQR)	-1.5 (-3.1 to -0.3)	-1.9 (-3.4 to -1.1)	-1.6 (-2.7 to -0.4)	-1.7 (-3.0 to -0.5)
Province, Outside Gauteng, <i>n</i> (%)	11 (16.9)	9 (19.1)	21 (24.4)	41 (20.7)
Inside Gauteng, <i>n</i> (%)	54 (83.0)	38 (80.8)	65 (75.5)	157 (79.2)
Gender Male, <i>n</i> (%)	28 (14.1)	33 (16.6)	45 (22.7)	106 (53.5)
Female, <i>n</i> (%)	37 (56.9)	14 (29.7)	41 (47.6)	92 (46.4)

Table 3.2 shows the aetiology of the CKD stages 3, 4 and 5 by age groups. Glomerular disease was the predominant cause of CKD in patients older than 5 years in 61 (43.5%). Overall, of the glomerular diseases nephrotic syndrome accounted for 35 (17.6%); 32 (91.4%) steroid resistant nephrotic syndrome (SRNS), two (5.7%) steroid sensitive nephrotic syndrome (SSNS) and one (2.8%) steroid dependent nephrotic syndrome (SDNS). The histological types were focal segmental glomerulosclerosis (FSGS) in 19 (54.2%), minimal change nephrotic syndrome (MCNS) in four (11.4%), congenital nephrotic in six (17.1%), and unknown in six (17.1%). HIVAN accounted for 22 (11.1%); two (9.0%) before year 2004 and 20 (90.9%) after year 2004.

The predominant cause in the 2-to-5-year age group was CAKUT in 25 (43.1%); posterior urethral valves (PUV) accounted for 28 (14.1%) overall.

Table 3. 2 Aetiology of CKD 3 to 5 by age groups

Age groups	2- 5yrs n (%)	≥5yrs n (%)	Total n (%)
Total	58 (29.3)	140 (70.7)	198 (100)
Glomerular disease	13 (22.4)	61 (43.5)	74 (37.3)
^a Nephrotic syndrome	10 (5.0)	25 (12.6)	35 (17.6)
HIV-Related Kidney Disease	2 (1.0)	20 (10.0)	22 (11.1)
^b Other	-----	12 (6.0)	12 (6.0)
Lupus nephritis	-----	4 (2.0)	4 (2.0)
APIGN	1(0.5)	-----	1 (0.5)
CAKUT	25 (43.1)	39 (27.8)	64 (32.3)
Posterior urethral valves	17 (8.5)	11 (5.0)	28 (14.1)
^c Other CAKUT	6 (3.0)	16 (8.0)	22 (11.0)
^d Other obstructive uropathy	1 (0.5)	7 (3.5)	8 (4.0)
Prune Belly Syndrome	1 (0.5)	5 (2.5)	6 (3.0)
Genetic Syndromes	9 (15.5)	14 (10.0)	23 (11.6)
Primary hyperoxaluria	5 (2.5)	11 (5.5)	16 (8.0)
Syndromic	1 (0.5)	2 (1.0)	3 (1.5)
ARPKD	2 (1.0)	-----	2 (1.0)
Cystinosis	-----	1 (0.5)	1 (0.5)
Nephronophthisis	1 (0.5)	-----	1 (0.5)
Voiding disorders	4 (6.8)	13 (9.2)	17 (8.5)
Neurogenic bladder	4 (2.0)	11 (5.0)	15 (7.5)
Dysenergetic bladder	-----	2 (1.0)	2 (1.0)
Acute kidney injury	5 (8.6)	4 (2.8)	9 (4.5)
CKD cause unknown	1 (1.7)	5 (3.5)	6 (3.0)
Vasculitis	-----	3 (2.1)	3 (1.5)
Primary hypertension	-----	1 (0.7)	1 (0.5)
Pyelonephritis	1 (1.7)	-----	1 (0.5)

HIV-Related Kidney Disease includes HIVAN (HIV nephropathy) (21,10.6%) and HIVIC (HIV-Associated immune complex kidney disease) (1, 0.5%); APIGN (Acute post-infectious glomerulonephritis); CAKUT (Congenital abnormalities of the kidney and urinary tract); ARPKD (autosomal recessive polycystic kidney disease).

^aNephrotic syndrome from causes other than HIV.

^bOther glomerular disease included the following: Immune complex glomerulonephritis (4,2%), tubulointerstitial nephritis (3,1.5%), membranoproliferative glomerular nephritis (2,1.0%), granulomatosis with polyangiitis (2,1.0%), IgA nephropathy (1,0.5%).

^cOther CAKUT included: dilated non-obstructed system (1,0.5%), horseshoe kidney (2,1.0%), multicystic dysplastic kidney (2,1.0%), hypoplastic dysplastic kidneys (2,1.0%), pelvic ureteric junction obstruction (3,1.5%), ureter stricture (2,1.0%), vesicoureteral reflux (6,3.0%), unilateral renal agenesis (4,2.0%).

^dOther obstructive uropathies included: urethral obstruction (1,0.5%), posterior urethra diverticulum (1,0.5%), megalourethra (1,0.5%), rhabdomyosarcoma (1,0.5%).

3.2. RISK FACTORS AT DIAGNOSIS

Risk factors for CKD were identified in 35 (17.6%) patients at diagnosis. In the 35 patients, low birth weight and prematurity was reported in 14 (40%), nine (25.7%) had antenatal hydronephrosis, seven (20%) had a positive family history of renal disease, two (5.7%) had AKI and three (8.5%) had other diagnosis which included small for gestational age (2, 5.7%) and birth asphyxia (1, 2.8%), see figure 3.2.

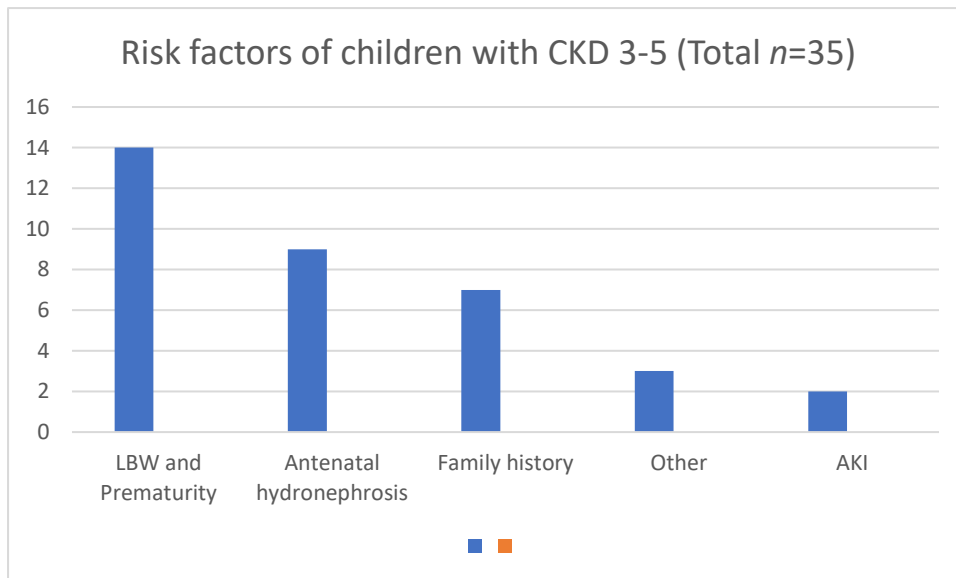


Figure 3. 2 Risk factors of children with CKD stage 3 to 5

3.3. COMPLICATIONS AT DIAGNOSIS

At diagnosis, 111 (56.0%) patients had hypertension. Hypertensive heart disease was documented in 63 (31.8%) on echocardiogram. No vascular calcifications were documented.

Table 3.3 shows the laboratory blood results at diagnosis. Haemoglobin, bicarbonate, and calcium were significantly lower in CKD stage 5 compared to CKD stage 3 and 4 at presentation, while serum phosphate, PTH and ferritin were significantly higher.

Table 3. 3 Laboratory results at diagnosis.

Variable	CKD stage 3	CKD stage 4	CKD stage 5	p-Value
	Median (IQR)	Median (IQR)	Median (IQR)	
Haemoglobin (g/dL)	11 (9.3 to 12.6)	10.4 (8.95 to 11.32)	8 (6.3 to 9.7)	0.0001
^a MCV (fL)	81.1 (75.9 to 85.6)	79.7 (76.6 to 83.5)	78.9 (73.9 to 82.8)	0.1179
Ferritin (ng/mL)	44 (22 to 184)	83 (46 to 293)	338 (152 to 671)	0.0001
Albumin (g/L)	32 (18 to 43)	38 (23 to 43)	29 (23 to 37)	0.1553
Bicarbonate (mmol/L)	16 (14 to 20)	13 (11 to 17)	11 (6 to 14)	0.0001
^b TSH (mIU/L)	3.7 (2.26 to 9.5)	4.44 (2.73 to 6.43)	4.38 (2.58 to 6.54)	0.9870
^c TC (mmol/L)	8.65 (6.49 to 12.4)	8.26 (4.2 to 9.41)	5.2 (3.79 to 7)	0.0004
Calcium (mmol/L)	2.28 (2.04 to 2.39)	2.3 (2.08 to 2.5)	2 (1.55 to 2.28)	0.0001
Magnesium (mmol/L)	0.85 (0.77 to 0.99)	0.93 (0.83 to 1.1)	0.94 (0.8 to 1.08)	0.2618
Phosphate (mmol/L)	1.70 (1.45 to 1.98)	1.67 (1.48 to 2.16)	2.23 (1.71 to 2.87)	0.0001
^d PTH (pmol/L)	10.25 (7.1 to 10.8)	17.1 (9.8 to 25)	45.1 (20 to 67.9)	0.0008

^aMean corpuscular volume, ^bThyroid stimulating hormone, ^cTotal cholesterol, ^dparathyroid hormone.

3.4. KIDNEY FAILURE TREATMENT OUTCOME

A total of 198 patients during the study period, 46 (23.3%) died, 59 (29.7%) were transferred to another unit, 69 (34.8%) were lost to follow up, 24(12.1%) were in active care

A total of 108 patients had CKD stage 5 at final outcome. Of the 69 (34.8%) patients lost to follow up, 22 (31.8%) had CKD stage 3 at final outcome, 17 (24.6%) had CKD stage 4 at final outcome and 30 (43.4%) had CKD stage 5 at final outcome.

Seventy-three (67.5%) patients received KRT and a total of 35 (32.4%) were treated conservatively. The different modality of KRT received is shown on Figure 3.3 below.

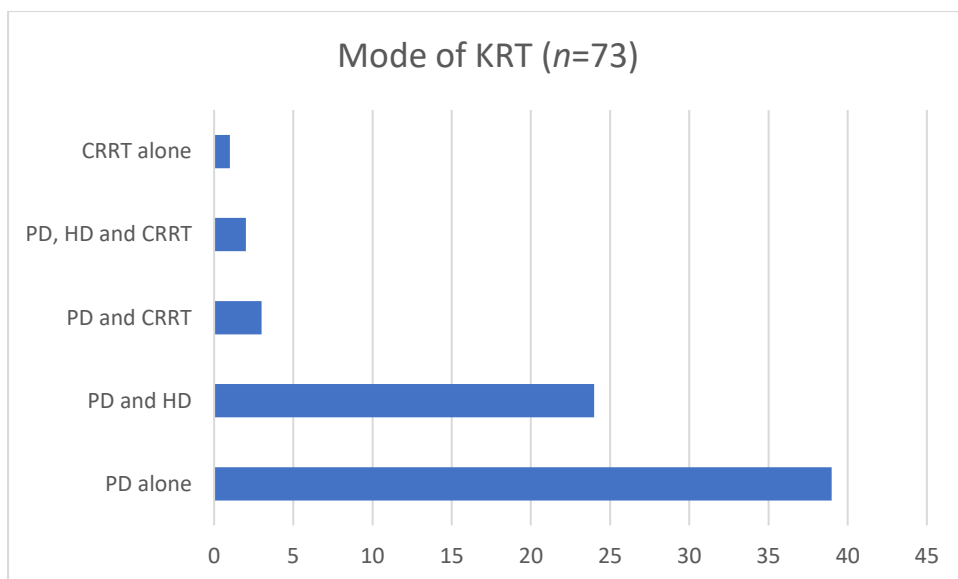


Figure 3. 3 Mode of kidney replacement therapy (KRT) at final outcome (n=73)

Patients with CKD can progress or improve from one CKD stage to another. With medical treatment the rates of progression may differ among institutions. Of the 86 children with CKD stage 5 at initial diagnosis, 79 (91.8%) remained in CKD stage 5 at final outcome. Likewise, of the 65 children with CKD stage 3 at initial diagnosis, 14 (21.5%) progressed to CKD stage 5. Forty-seven children had initial CKD stage 4, of those 15 (31.9%) progressed to CKD stage 5. This resulted in a total of 108 children with CKD stage 5 at final outcome as seen in Table 3.4.

Table 3. 4 Progression of CKD from initial stage at diagnosis to CKD stage at final outcome.

CKD stage at initial diagnosis	CKD stage at final outcome				Total rows
	CKD 2	CKD 3	CKD 4	CKD 5	
CKD 3	0	39	12	14	65
CKD 4	1	2	29	15	47
CKD 5	1	3	3	79	86
Total column	2	44	44	108	198

The mean rate of decline in eGFR from baseline to final visit was 4.90 (SD 7.03) ml/min/BSA per year.

3.5. FACTORS ASSOCIATED WITH MORTALITY

The median (IQR) duration of follow up was 1.2 (0.3 to 3.2) years. The mortality rate was 9.8 (95%CI:7.3-13.1) person-years (PY), contributed by 46 (23.3%) children. The 9.8% is derived from the number of people who died and their contributed time i.e. for every 100 people, 10 of them die. For factors associated with mortality determined by the adjusted Cox regression, patients with CKD stage 5 had 3.5 times (95%CI:1.5-7.9, p-value 0.002) increased risk of death compared to those with CKD stage 3. Patients with albumin <25g/L had 2.6 times (95%CI:1.0-6.2, p-value 0.030) greater risk of death compared to those with albumin $\geq$ 25g/L. Patients with glomerular disease had 2.5 times (95%CI:1.0-6.3, p-value 0.046) risk of death compared to those with CAKUT.

The final adjusted model was assessed for the proportional hazard assumption using the Schoenfeld residuals and the global test gave a p-value=0.1921 which indicates that the proportional hazards assumption was satisfied. Table 3.5 shows variables associated with mortality in patients with CKD stage 3 to 5.

Table 3. 5 Cox Regression Analysis for variables associated with mortality

	<i>n</i> (%)	Univariate Cox regression		Adjusted Cox regression	
	46	HR (95%CI)	P-value	Adjara (95%CI)	P-value
Gender Female Male	24(52.1) 22(47.8)	1(ref) 0.6(0.3-1.1)	0.111	-----	-----
Age group 2-5 years ≥5 years	11(23.9) 35(76.0)	1(ref) 1.5(0.7-3.1)	0.193	-----	-----
Residence In Gauteng Outside Gauteng	34 (73.9) 12(26.0)	1(ref) 1.7 (0.9-3.4)	0.096	-----	-----
CKD stage 3 4 5	9 (19.5) 6 (13.4) 31(67.3)	1(ref) 1.0 (0.3-2.8) 3.8 (1.8-8.2)	0.977 <0.001	1 (ref) 1.09 (0.3-3.1) 3.5 (1.5-7.9)	0.863 0.002
Disease Glomerular CAKUT Other	25 (54.3) 11 (23.9) 10 (21.7)	4.1 (1.9-8.7) 1(ref) -----	<0.001	2.5(1.0-6.3) 1 (ref) -----	0.046
Haemoglobin <11g/dL ≥11g/dL	38 (82.6) 8 (17.3)	2.6 (1.2-5.7) 1(ref)	0.012	-----	-----
Serum albumin <25g/L ≥25g/L	20 (43.4) 26 (56.5)	4.0 (2.1-7.4) 1 (ref)	<0.001	2.6 (1.0-6.2) 1 (ref)	0.030
Serum bicarbonate <22mmol/L ≥22mmol/L	43 (93.4) 3 (6.5)	3.5 (1.0-11.5) 1 (ref)	0.035	-----	-----
Proteinuria <2 plus ≥2 plus	14 (30.4) 32 (69.5)	1 (ref) 2.5 (1.3-4.7)	0.005	-----	-----

One event time was indeterminate for a female child with CKD stage 5 cause unknown and thus excluded from the Cox regression analysis.
One is equivalent to the reference (ref).

The Kaplan-Meier curve for CKD stages shows that more deaths occurred among patients in Stage 5 (Figure 3.4), and those with glomerular disease (Figure 3.5).

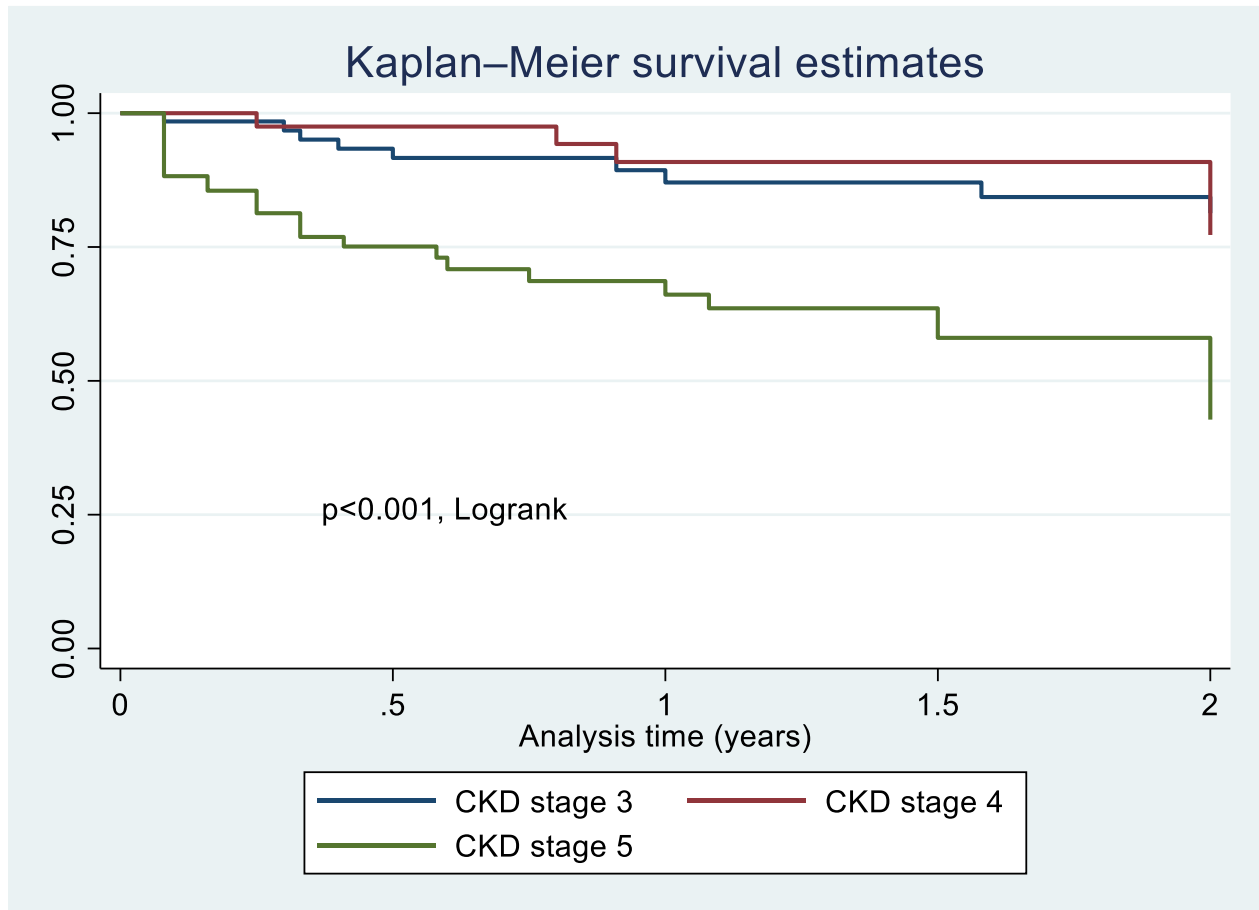


Figure 3. 4 Kaplan-Meier survival estimates of CKD stages over a two-year period after diagnosis

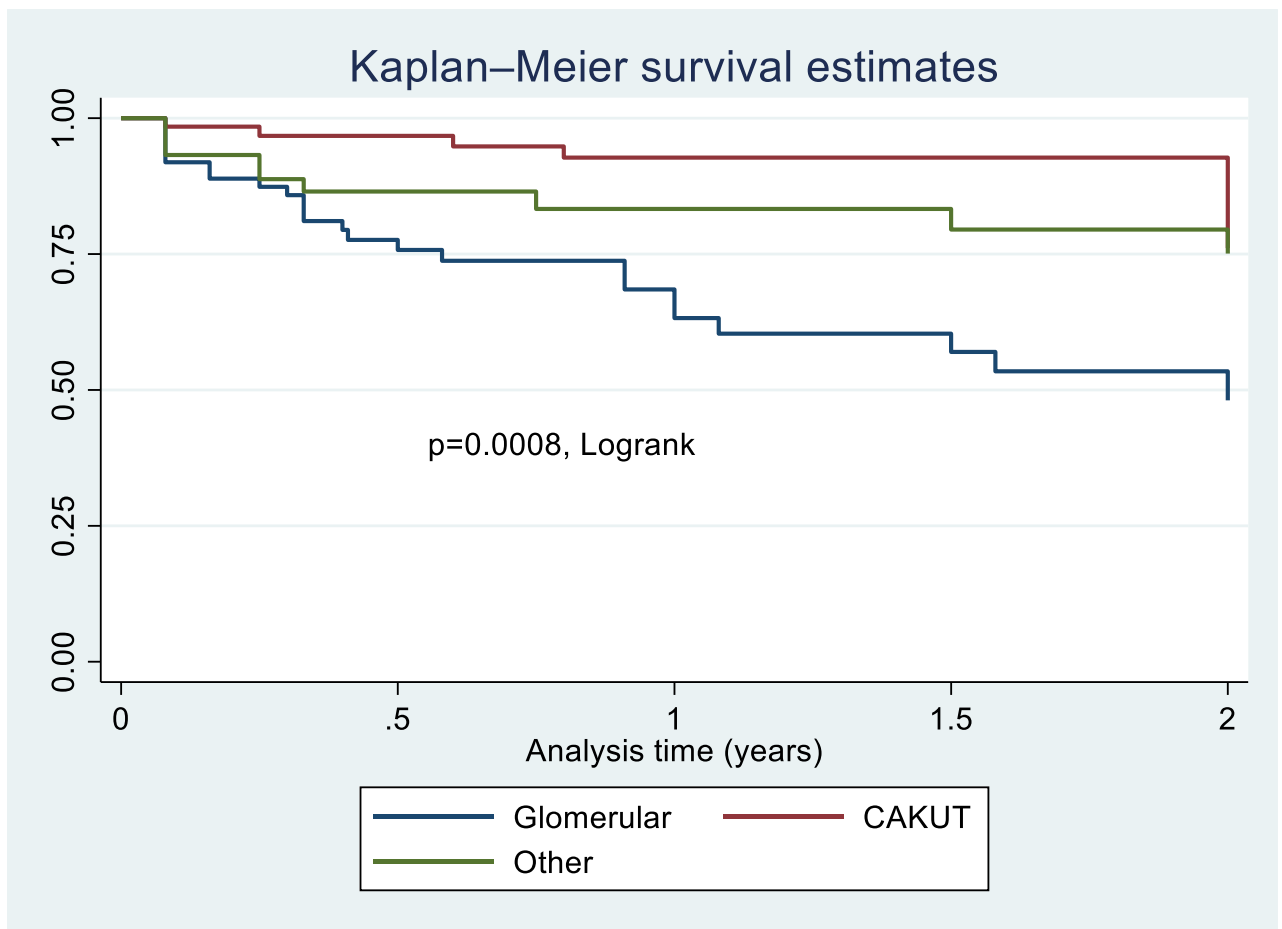


Figure 3. 5 Kaplan-Meier survival estimates of CKD aetiology over a two-year period after diagnosis.

CHAPTER FOUR – DISCUSSION

4.1. DEMOGRAPHICS AND EPIDEMIOLOGY

This study addresses some of the research gaps in South African children with CKD. It provides a calculated incidence rate of CKD stage 3-5 for children in a SA setting, using age-appropriate population indices as supplied by the DHIS. The calculated incidence in our study, for year 2001 to 2019 ranged from 9.3 to 29.7 pmarp. This is higher than other SA studies of CKD in children reporting an incidence of 1–2 per million age-related population in their region (17). The difference could be explained by the different study methods employed.

The calculated incidence rate is similar to the incidence of CKD in children in Europe which is stated to be around 11–12 per million of age-related population (pmarp) for stages 3–5 (56). In the ItalKid project, the mean incidence during the period 1995–2000 was 12.1 cases pmarp (range: 8.8–13.9). This however included children with stage 2 CKD ($\text{Ccr} < 75 \text{ mL/min/1.73m}^2$) (57).

Incidence rates can be affected by inaccurate values in the numerator or denominator. It may be underestimated by those patients not referred to our centre, missed diagnosis or those seeking alternative medicine. Despite these limitations, this calculated pmarp incidence rate of CKD in children aged two-to-14-year-old in our study should assist Health Economists as South Africa moves to Universal Health Coverage (UHC) and endeavour to attain sustainable developmental goals (SDG) (2).

The median age at diagnosis of CKD stage 3 to 5 in our study was 7 (4-11) years. In the ItalKid project, the mean age at registration was 6.9 ± 5.4 years (57). They included patients less than 20 years at the time of presentation and the eGFR using the Schwartz's formula was $< 75 \text{ mL/min/1.73m}^2$ (pre-dialysis). Despite a broader inclusion criterion used in the ItalKid project, the ages at registration are similar. In a local study by von Biljon on pre-pubertal children with CKD stages 2 to 4, the mean age at presentation was 4.83 (SD 2.53). Interestingly, in this study, children with non-glomerular disease presented at a younger age compared to those with glomerular disease (58). Similarly, in our study, glomerular disease was the predominant cause of CKD in patients older than 5 years.

In our study, CKD was mostly prevalent in males. This may be due to more congenital abnormalities of the kidney and urinary tract (CAKUT) being prone in males (56).

More than 50% of patients referred from outside Gauteng province in our study had CKD stage 5 at presentation. This reflects late referrals, possibly due to delayed presentation or missed diagnosis. Patients are referred from other provinces such as Northwest Province (NWP) due to lack of renal services outside of Gauteng Province. Chronic kidney disease is silent before the late stages, which is another factor in delayed presentation.

Patients in our cohort present in advanced stages of CKD with high mortality and morbidity rates, typical of sub-Saharan African countries (1). In a study done in a tertiary hospital in Malawi, 56% of patients presented with CKD stage 3 to 5 (12) and another study in a paediatric renal unit in Cameroon, CKD stage 5 was the most frequent (81.3%) presentation (59). This data identifies a potential area of intervention to improve patient outcomes to meet the SDG.

4.2. AETIOLOGY

4.2.1. NEPHROTIC SYNDROME

In our study, glomerular disease is the most common cause of CKD stages 3 to 5 in children above 5 years of age (43.5%) as well as overall (37.3%), similar to other studies from South Africa and Nigeria (12, 13, 17, 60). This is however contrary to other recent reports from South Africa and Pakistan stating CAKUT as the most common cause in children with CKD (53, 61, 62). This may be due to different study periods and temporal changes in healthcare associated with outcomes. While congenital structural causes such as renal hypoplasia and posterior urethral valves (PUV) are more prevalent in the younger age groups, the incidence of glomerulonephritis does increase in those >12 years of age (56). In a study done in SA, KwaZulu Natal (KZN) on stage 2 to 5 in children, the commonest cause of CKD in all children was nephrotic syndrome, amounting to 36.5% overall (17). This is similar to our study where nephrotic syndrome (37.3%) is followed by CAKUT (32.3%) and genetic syndromes (11.6%) of which primary Hyperoxaluria contributed the most (8.0%). Glomerular disease is more prevalent than other renal diseases in Africa and the commonest form of presentation is nephrotic syndrome with age of onset at five to eight years (63). In a single centre study by

Wong et al. in Canada reports glomerular disease accounting for 27% of the overall causes of CKD compared with uropathies, which accounts for 31.1% (64). In Italy, CKD is largely caused by CAKUT (49.1%), steroid-resistant nephrotic syndrome (10.4%), chronic glomerulonephritis (8.1%) (e.g., lupus nephritis, Alport syndrome) and renal ciliopathies (5.3%) (56).

In our study, most children with CKD due to underlying nephrotic syndrome have focal segmental glomerular sclerosis (FSGS) on kidney biopsy. Globally, most children with SRNS have FSGS on kidney biopsy (31). In our study 91.4% of children had SRNS. In a study using the NAPRTCS database, using obstructive uropathy as the referent group, FSGS is the only diagnosis independently associated with a risk of disease progression (HR, 1.77; 95% CI, 1.48 to 2.12) (65).

Two hundred genes are identified to cause the most common aetiologic spectrum of CKD in children, including SRNS; genetic testing is not routinely available in SA. Genetic testing has substantial implications such as prenatal testing in affected siblings, genetic counselling and in assessing the patient's prognosis (56). Genetic testing may identify patients in whom immunosuppression for nephrotic syndrome is futile. This is an area of future research which potentially could alter patient outcomes with regard to infections due to immunosuppressive therapy.

4.2.2. HIV ASSOCIATED NEPHROPATHY (HIVAN)

Most patients in our study with HIV related kidney disease were diagnosed between years 2010 and 2019. The number of children with CKD stage 3 to 5 and HIV infection in the four-year period prior to 2004 in our study is 9.0% and 90.9% in the sixteen-year period from 2004 to 2019 when anti-retroviral (ARV) treatment became available (24). This may reflect the success of the ARV program in preventing early mortality in these patients.

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In our study, all patients with CKD due to underlying HIV related kidney disease were diagnosed with a kidney biopsy. A total of 22 (11.1%) of children had HIV related kidney disease in our study of which 21 (10.6%) had HIV associated nephropathy (HIVAN) and 1 (0.5%) had HIV immune complex kidney disease (HIVICK). This is more than reported in the study by Imani et al who demonstrates a prevalence of 1.6% of children with CKD and HIV in

their sub-Saharan cohort (66). This may be due to a shorter study period of 6 years in their study or earlier implementation of antiretroviral drugs.

4.2.3. CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT (CAKUT)

In our study, PUV is the most common cause of CAKUT (14.1%) and mostly diagnosed in children 2 to 5 years of age (8.5%). This is similar to a study at a main tertiary paediatric renal centre in Cameroon where of the urological malformations, PUV is the most common cause of CAKUT (59). In a study at a tertiary hospital in Malawi, all patients presenting with obstructive uropathy had eGFR <60ml/min/1.73m² (12). This highlights the late diagnosis or presentation in LMIC countries and the importance of early intervention (12). Considering that CAKUT are the leading cause of CKD in children below age 5 years at diagnosis, foetal anomaly scans, screening ultrasound in children with documented urinary tract infection (UTI), and early referral will allow timeous interventions to prevent CKD (29, 40, 59).

4.2.4. PRIMARY HYPEROXALURIA

In our study, Primary Hyperoxaluria is the most common genetic syndrome (8.0%) and presenting mostly above the age of five years. Primary Hyperoxaluria type 1 (PH1), a rare autosomal recessive condition, is the most frequent and severe form of primary hyperoxalurias, leading to end-stage kidney disease (ESKD) and systemic organ damage (41, 67). One major hallmark of PH1 in both LMIC and HIC is the delay in diagnosis averaging five years from initial presenting symptoms to diagnosis (67). Chang et al at CHBAH also showed that the median (IQR) age of presentation is 72.0 (44.0-108.0) months and nephrocalcinosis is significantly associated with KF ($p=0.009$) (41). The most common presentation in Chang et al. was urolithiasis, with or without nephrocalcinosis, urinary tract infections (UTIs), haematuria and KF (41). Screening urine dipstick at primary health care centres or school clinics is a potential public health care tool to identify CKD early.

4.2.5. ACUTE KIDNEY INJURY (AKI)

Although AKI may progress to ESKD, it is seen in a few of the patients with CKD stage 3 to 5 in our study. It is possible that patients diagnosed with mild stages of AKI or who have partial recovery of renal function are not referred to the renal services in our centre. Another reason

may be related to the high mortality of AKI in low resource settings (68). Communicable diseases causing septicaemia and diarrhoeal diseases resulting in hypovolemia and septic shock, herbal medication from alternative medicine and malaria are common in LMIC and have a role in causing AKI (59). Most patients in a study in a tertiary hospital in Malawi with AKI show improvement in their glomerular filtration rate and a minority progress into CKD stage 3 (12). In an adult review article by Coca et al. reports that AKI increases the risk of CKD by 8-fold (HR 8.8, 95% CI 3.1–25.5) and the risk of end-stage kidney disease by 3-fold (HR 3.1, 95% CI 1.9–5.0) (69). A review study of AKI in children and adults in sub-Saharan Africa, reported that 1042 of 1572 (66%) children needed acute dialysis, five (0.8%) of these children progressed to CKD (68). Raising awareness of AKI and implementing appropriate screening tools for progression to CKD are possible areas of interventions to improving outcomes.

4.3. RISK FACTORS

In our study risk factors were identified in 35 (17.6%) patients. The retrospective nature of the study could be under- representing risk factors. Most of the risk factors could be identified in the neonatal period. This represents an opportunity for intervention and screening starting in the neonatal period.

In general, risk factors for CKD include small for gestational age, low birthweight and prematurity and are more common in LMIC. These perinatal conditions increase the risk of proteinuria, hypertension, and CKD in later life (29, 70, 71, 72, 73, 74) through multiple methods including low nephron numbers (70, 71, 72, 73, 74).

Interestingly in the CKiD cohort, the rate of change in GFR over time did not differ significantly between children with abnormal birth history (defined as SGA, birthweight < 2500 g, or gestational age < 36 weeks) and those without thus suggesting that other factors may be at play. (75).

Strategies could be implemented in neonatal outpatient clinics to screen patients with risk factors for chronic kidney disease and early referral to nephrology services.

4.4. COMPLICATIONS

In our cohort, complications of CKD at initial diagnosis significantly progressed with advancing stage of CKD

4.4.1. ANAEMIA

Anaemia in children with CKD is a serious complication leading to decreased ability of daily activities such as exercise and cognitive abilities, thus leading to poor quality of life (56). It also causes progression of cardiovascular risk factors such as left ventricular hypertrophy (LVH) (56). As in adults, the goal of treatment is to achieve target haemoglobin levels of approximately 11 g/dL or slightly greater. (56).

In our study, anaemia ($p=0.0001$) is more prevalent in children with CKD stage 5 [8g/dL (6.3 to 9.7)] compared to CKD stage 3 [11g/dL (9.3 to 12.6)] and stage 4 [10.4g/dL (8.95 to 11.32)].

This underscores the need for screening, as early diagnosis of CKD provides an opportunity to treat the anaemia and its complications.

In a single centre study by Wong et al., anaemia was present in 36.6% of the overall cohort. The prevalence of anaemia increased from 31% at stage 1 to 93.3% ($P<0.001$) at stages 4 and 5 (64). Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) shows that the prevalence of anaemia in children was 73% at CKD stage III, 87% at stage IV and >93% at stage V (56). In another local study by Mudi et al., there was a high prevalence (41/130; 32%) of anaemia among the patients with CKD stage one to five (46).

In our study the serum ferritin is significantly greater in the patients with CKD stage 5, likely signifying an inflammatory response or due to blood transfusions (56). It is not uncommon for patients with CKD to have normal or elevated ferritin levels as a sign of inflammation and not necessarily total iron body stores (56). Supplemental iron therapy (either oral or intravenous) is necessary for the treatment of anaemia in children with CKD (45). Data on iron supplementation was not collected in our study. In a local study by Mudi et al. (46), serum ferritin and RCDW were the only independent predictors for anaemia, iron deficiency and iron deficiency with anaemia ($p<0.050$) (46). There are other important causes of anaemia including erythropoietin (EPO) deficiency (46). These were not assessed in our study.

Despite use of EPO, iron supplementation and blood transfusions, anaemia is difficult to correct even in HIC (56). Heparin has an important role in contributing to anaemia in patients with CKD. It is a peptide produced in the liver and is inappropriately high in patients with CKD and thus leading to increased iron storage (high ferritin) and decreased free iron for erythropoiesis (low serum transferrin saturation (TSAT)). The hypoxia-inducible factor (HIF) pathway is also essential in inducing erythropoiesis (76). This has been an area of research and newer agents have become available (76).

Anaemia is a risk factor for mortality, discussed in the next section 4.6.

4.4.2. METABOLIC ACIDOSIS

Epidemiologic studies demonstrate that lower serum bicarbonate is associated with an increased risk of kidney disease progression (77). In our study, the median serum bicarbonate value decreased significantly with advancing stages of CKD. This reflects progression of metabolic acidosis in more severe forms of CKD stages.

In our study, a serum bicarbonate <22 mmol/L is a significant risk factor for mortality in the univariate analysis ($p=0.035$) but not in the multivariate analysis. In a single centre adult retrospective cohort study involving patients with kidney disease of which 9% with a baseline eGFR <60 ml/min/1.73m², the risk of CKD progression i.e., decline in the eGFR by 50% or reaching an eGFR of <15 ml/min/1.73m², in the multivariate analysis was 1.54 (95% CI: 1.13-2.09) with bicarbonate levels <22 mEq/L compared with bicarbonate levels of 25 to 26 mEq/L (78).

Metabolic acidosis is also observed in earlier stages of CKD, especially in renal disease with tubular dysfunction such as CAKUT or chronic tubulointerstitial nephritis (79). This represents an area of research into optimization of acid-base in children with CKD to slow down progression.

4.4.3. MINERAL AND BONE DISORDER

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is represented by abnormalities in calcium, phosphate, parathyroid hormone (PTH) and Vitamin D metabolism. This affects children's linear growth and can cause vascular or soft tissue calcifications (56). Renal osteodystrophy, another feature of CKD-MBD, is diagnosed by histology (56).

In our study none of the patients had vascular or soft tissue calcifications documented. Our study shows significant progression of calcium ($p=0.0001$), phosphate ($p=0.0001$) and parathyroid hormone ($p=0.0008$) abnormalities with increasing CKD stage, with severity increasing in patients with CKD stage 5. This highlights disease severity with progressing stages of CKD. In the single centre study by Wong et al., the prevalence of metabolic bone disease was as high as 15% in stage 2 disease, 47% in stage 3, and 100% in stages 4 and 5 CKD (64). In a study using the NAPRTCS database, patients with hypocalcaemia at time of registration had a 29% higher risk for renal progression independent of other factors (HR, 1.29; 95% CI, 1.06 to 1.58) compared to patients with normal serum calcium. In addition, hyperphosphataemia posed a 41% increased risk of renal progression compared to normal serum phosphate, (HR, 1.41; 95% CI, 1.25 to 1.59) (65). Prospective studies at our site may provide more accurate prevalence of CKD-MBD.

The reason for emphasis on prompt management of CKD-MBD is to slow down stunting as well as bone remodelling. More importantly, phosphate is a potent vascular toxin by itself or by its effect on PTH and fibroblast growth factor 23 thus leading to progression of cardiovascular disease as emphasized below (56).

4.4.4. CARDIOVASCULAR DISEASE

One of the most important aims of treating complications of CKD is to reduce the cardiovascular risk of death. As in adults, cardiovascular disease (CVD) is the leading cause of death in the paediatric CKD population, with a risk 1000 times higher in the ESKD group compared with paediatric group without CKD. (56).

In our study, at diagnosis, 111 (56.0%) patients had hypertension. Hypertensive heart disease was documented in 63 (31.8%) on echocardiogram.

Risk factors for cardiovascular disease in children with CKD include steroid therapy, as well as risk factors specific for CKD such as hyperphosphataemia, hyperparathyroidism and anaemia (56). This can lead to mortality from cardiac arrest due to arrhythmias, valve disease and cardiomyopathy (56).

4.5. KIDNEY FAILURE TREATMENT OUTCOME

In our study, seventy-three (67.5%) patients received KRT. Most of the patients in our study received peritoneal dialysis. Peritoneal dialysis is still the first choice of dialysis in our cohort as is also represented in most countries with limited resources, including South Africa (18, 80)

It is estimated that annually at least 1,000 children might require KRT in South Africa (81). However less than 10% are estimated to being able to get access to KRT in South Africa (81).

Although in South Africa access to KRT is state- funded and is supposed to be accessible to all children, the reality is that the financial burden placed on the family of a child with ESKD becomes insurmountable (81). This is compounded for patients travelling from provinces where paediatric nephrology services are not available. Even for those children who have access to private health insurance, the non-medical cost burden on the family can still be significant leading to a need for social and financial assistance (81). A total of 35 (32.4%) of patients in our study were treated conservatively. The underlying factors leading to CKM were not explored in this study. The Pediatric Feasibility Assessment for Transplantation (pFAT) tool developed at Red Cross Children's Memorial Hospital allows standardization of eligibility of children with CKD for transplantation in a resource limited setting (53). Children can be excluded from the chronic dialysis and transplant program in most tertiary institutions including CHBAH for various reasons such as parents' choice, poor social circumstances, distance from centre, severe illness and non-South African nationality. This is decided upon after careful discussions in a multi-disciplinary team with the family. Conservative kidney management is regarded globally as one of the active treatment modalities for patients in kidney failure in addition to dialysis and kidney transplant (52). It is not regarded as "doing nothing", instead it aims at slowing the progression of kidney disease and managing the complications of disease (52).

Our study demonstrated a mortality rate of 23.3% and a high lost to follow up percentage of 34.8%. In addition, most of the patients lost to follow up had CKD stage 5 at final outcome (43.4%) therefore potentially confounding the mortality rate. Reasons for this could be patients seeking alternative medicine, distance from renal centres or early death from complications of CKD. In the study in Cameroon by Halle et al reports a mortality rate of 50%, their mortality rate could be explained by severity and type of renal disease at presentation and lack of chronic dialysis infrastructures and affordability (59). This is similar to a systematic review in sub-

Saharan Africa done by Ashuntantang et al., in both adults and paediatrics patients with ESKD which showed a mortality rate of 62% in the paediatric population (82). Compared to other African countries, dialysis in South Africa is state funded thus allowing the children to have better access to KRT and thus contributing to our lower mortality rate. However, it should be noted that the mortality rate in our cohort may be underestimated because the outcome of patients transferred to the transplant centre is not known as well an assumption that the 43.4% of children lost to follow up with CKD stage 5 at final outcome, died.

4.6. RISK FACTORS FOR MORTALITY

In our study, glomerular disease, hypoalbuminaemia, and CKD stage 5 at presentation is a significant risk factor for mortality in the multivariate analysis, increasing the risk of mortality by 2.5, 2.6 and 3.5-fold respectively. This is similar to other studies (43, 62, 83, 84). Kamath et al. on multivariate analysis, identified glomerular disease amongst other variables to be a risk factor for progression of CKD (84). On the Kaplan-Meier survival curves in our study, patients with glomerular disease had greater mortality over time compared to those with CAKUT. This supports the notion of slower advancement to ESKD in patients with CAKUT, compared to those with glomerular diseases (56).

The mean rate of decline in eGFR from baseline to final visit in our study of 4.90 (SD 7.03) ml/min/BSA per year, was similar to the study by Soares et al. which reported a rate of 5.8 (SD 12.4) ml/min/BSA per year (85). In a local study by van Biljon, the rate of decline in GFR in pre-pubertal children with glomerular vs non-glomerular disease, was more than 5 mL/min/1.73 m²/year in 82% of patients with glomerular compared with 5% with non-glomerular disorders (58). The mean rate of decline in the eGFR in our study was however higher compared to the study by Kamath et al., which reported a median rate of 3.5 (IQR 1.7, 11.00) ml/yr (84). This may be due to inclusion of CKD stage 2 in their study as well as a short follow up period (84).

Anaemia and proteinuria are documented risk factors for mortality in children with CKD (65, 86). In our cohort, although identified as risk factors on univariate analysis, significance is not demonstrated on multivariate analysis.

4.7. STUDY STRENGTHS AND LIMITATIONS

The study is limited by its retrospective nature and missing information on outcomes for patients who have not returned for scheduled appointments, i.e. lost to follow up. Referral bias may overrepresent certain diagnoses, and patients not referred or who died at the peripheral hospitals may underestimate the incidence rates. Despite these limitations, the strength of this study is the ability to demonstrate the spectrum of CKD in children over two decades. This study demonstrates a calculated annual incidence rate of CKD stage 3 to 5 in children. The study describes the risk factors associated with mortality and makes clear recommendations for interventions and areas of research in prospective studies.

CHAPTER FIVE – CONCLUSION

The spectrum of chronic kidney disease is predominantly glomerular in our population, similar to other countries in Africa and Sub-Saharan Africa (12-13, 17, 19, 60, 63). This study highlights the need for screening programs for the general paediatric population, particularly those of pre-school going age for glomerular diseases and re-enforcing antenatal screening for CAKUT and early management of both diseases.

The calculated incidence in our study is higher than previously stated in other South African studies (17). The high incidence is concerning because it is only a reflection of the proportion of referrals to our facility and excludes those that are not referred. The calculated incidence reflects a burden of CKD not previously documented in South Africa and Africa (81).

Even though South Africa is labelled an UMIC, the reality is 85% of the population depends on the limited resourced public health care system (18, 81). This is further compounded by the limited number of trained paediatric nephrologists in South Africa, most of whom are found in tertiary health care centers thus leaving the peripheral hospitals in other provinces without paediatric renal expertise. The lack of service, early detection and adequate referral pathways for renal children contributes to late referrals (87). In addition, the social determinants of health, health-seeking behaviour, cultural and religious beliefs all impact on delayed diagnosis and compliance of follow-up (17). Unfortunately, these factors also impact on the feasibility for kidney transplantation (53), which may partially explain the rate of conservative therapy in this population. Low- and middle-income countries are challenged not only by lack of renal centres, but also by the limited resources such as dialysis (64, 81).

Our study demonstrated that the mortality in patients within our region is high and potentially underestimated by the unknown outcomes of the children lost to follow up and those transferred to other facilities. The mortality in our study also demonstrated significant association with glomerular disease, hypoalbuminemia and children presenting late in end stage kidney disease. The Department of Health in South Africa emphasises the importance of acting decisively to prevent and combat non-communicable diseases, including kidney diseases (88, 89). This is important as South Africa moves into Universal Health Coverage as well as fulfilling the SDG in 2030. It is proposed that all concerned, including government and nonstate actors, must put

more effort into prevention and guidelines on screening and treatment of kidney disease (89). The results of this study may provide guidance in this regard.

5.1. RECOMMENDATIONS

This study proposes the following recommendations to identify kidney disease early with appropriate referral to nephrology specialist services:

- 1) Implement targeted screening programs at the primary health care level using urine dipstick and blood pressure readings to identify glomerular disease or CKD early in order to implement early preventative treatment.
- 2) Neonates with known risk factors such as prematurity, neonatal AKI, birth asphyxia, family history of kidney disease, abnormal foetal anomaly scan could be screened at neonatal follow-up clinics for chronic kidney disease.
- 3) Inpatients diagnosed with AKI should be screened for CKD and have time to progression to CKD documented.
- 4) Training of paediatric nephrologists in provinces where these services are not available which may decrease late referrals and disease severity upon presentation.

5.2. FUTURE RESEARCH

Future research such as prospective studies on the influence of hypertension in children with CKD in our regions is important and was not investigated in our study. It is also important to look at the cause of death and kidney transplantation rates in children with moderate to severe CKD. Research is recommended on the epidemiology of CKD in children under two years of age. A national Paediatric CKD registry including the patients managed conservatively will provide valuable data on the current situation. These studies should focus on the development of protocols to help alleviate the burden of this disease in South Africa. Studies exploring the psychosocial burden on families are underway in the unit. Other areas of potential research include obtaining funding for genetic testing for various kidney conditions, prospective follow up studies on early screening of risk factors in the neonatal period and its association with eGFR decline rates, and research on early optimization of hypoalbuminaemia in CKD and outcomes on patient mortality.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG



R14/49 Dr Nokukhanya Ngubane-Mwandla

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210468

NAME: Dr Nokukhanya Ngubane-Mwandla
(Principal Investigator)
DEPARTMENT: Paediatrics
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: A descriptive study of chronic kidney disease (stages 3-5) in children at Chris Hani Baragwanath Academic Hospital, 2000-2019

DATE CONSIDERED: 30/04/2021

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof K. Petersen

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

DATE OF APPROVAL: 28/06/2021

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 **April** and will therefore be due in the month of **April** 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 B: FACULTY PROTOCOL APPROVAL LETTER



Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

Dr NA Ngubane-Mwandla
P O Box 762
Wilgeheuwel Ext 3
1736
South Africa

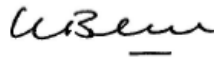
15 February 2024
Person| No: 1332856
PAG

Dear Dr Nokukhanya Ngubane-Mwandla

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *A descriptive study of chronic kidney disease (stages 3-5) in children at Chris Hani Baragwanath Academic Hospital, 2000-2019* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely



Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

PROTOCOL ASSESSORS MEETING

Candidate Full Name: . Dr NAN Ngubane-Mwandla.
.....

Student Number: . 1332856. Date: ...17 May
2021

School / Department / Division: . Division of Paediatric Nephrology, Department of Paediatrics and
Child Health, School of Clinical Medicine
.....

1. Type of study (tick all that apply):

- ☒ Quantitative
- ☐ Qualitative
- ☐ Mixed Methods
- ☐ Laboratory
- ☐ Clinical
- ☐ Other, please
specify.....

2. Is title of the study appropriate (preferably fewer than 20 words)?

Yes	No
-----	----

Comments:

3. Are the study objectives clear and linked to the research aim and title?

Yes	No
-----	----

Comments:

- The Objectives are clear
- There is confusion with the Research Question (assuming the research question and the title are synonymous) and aim of the study; they are just repeated

4. Is the design of the study appropriate to meet the study objectives?

Yes

No

Comments:

- Is 120 patients over 20 years correct?

5. Are the proposed methods and tools appropriate to meet the research objectives?

Yes

No

Comments:

- Exclusion criteria – explain why children less than 2 years old are excluded from your study; this is mentioned briefly in the literature review
- Include the patients less than 2 years of age to improve your patient sample

6. Is the study feasible within the resources of:

a) The applicant?

Yes

No

b) The department?

Yes

No

c) The time frame?

Yes

No

7. If this is a PhD protocol assessment:

a) Is the content original?

Yes

No

b) Does the content show the scope and depth of a PhD?

Yes

No

Comments:

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:

- This protocol is being submitted for the purposes of achieving a MSc degree.
- What are the requirements of this degree (eg division between course and research)
- Is the research question and scientific methods adequate for achieving a MSc
- Costs: are the costs of registering for this degree not born by the candidate?
- What are the strengths of this research protocol?
- Database: are you considering other referrals? (is it only those 3 hospitals) Age at presentation is 1-<5 but 2 year olds are excluded.

- Grammatical and typographical errors (minor)

ii. The appointment of the proposed Supervisor?

Yes	No
-----	----

Nominee/s: Prof K. Petersen_____

iii. The appointment of the proposed Co-Supervisor/s and/or additional co-supervisors?

Yes	No
-----	----

Nominee/s: Dr N. Lala_____

iv. Has the Chair of the Assessor Group signed the RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS form? Please attach.

Yes	No
-----	----

v. Has the Chair informed the student and supervisor about the Wits ethics requirements, and that if required, they must have either a Wits Human Research Ethics clearance certificate or a Wits Animal Research Ethics clearance certificate?

Yes	No
-----	----

vi. Based on the protocol provided (including any proposed changes by the protocol assessor group),

does the student require:

1. **Human Research Ethics clearance certificate**
2. Animal Research Ethics clearance certificate
3. No human or animal ethics certificate is required
4. Unclear, will seek appropriate guidance from the HREC/AREC committees

vii. Has the Postgraduate student and supervisor/s signed the ethics declaration form

Yes	No
-----	----

Yes	No
Yes	No
Yes	No
Yes	No

Overall recommendation regarding the protocol:

- i. Revision of the protocol to the satisfaction of the Supervisor (**NB: if HoD approval is also required, please specify**):

Yes	No
-----	----

(Candidate: one copy, list of corrections with page numbers and Supervisor approval letter – submit to PG Office).

- ii. Revision of the protocol to the satisfaction of the Assessor Group/Chair:

Yes	No
-----	----

(Candidate: one copy, list of corrections with page numbers, Supervisor approval letter – submit to PG Office and PG Office to forward to the Assessor Group Chair).

- iii. Revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting:

Yes	No
-----	----

(Candidate: six copies, list of corrections with page numbers, Supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator / for PhD, all six copies to be submitted to the PG Office).

- iv. Candidate goes ahead (no revision required):

Yes	No
-----	----

Details of Assessors:

Name:	Email:	Sign:
Dr.Priya Walabh		
Dr Basetsane Moraone	basetsana.marokane@wits.ac.za	
Dr Thuso		
Prof Z Mohammed		

Details of Assessor Group Chair:

Name:	Email:	Sign:
Dr Shaegan Irusen	Shaegan.irusen@wits.ac.za	

Date: __26 May 2021_____

APPENDIX C: DEFINITIONS

CHRONIC KIDNEY DISEASE (CKD)

Either of the two must be present for >3months:

1. Markers of kidney damage (one or more) must be present for >3 months, including the following:
 - Proteinuria $\geq 2+$
 - Microscopy on urine sediment abnormalities.
 - Abnormalities detected by histology.
 - Structural abnormalities detected by imaging.
2. GFR <60 ml/min/1.73 m² (GFR categories G3–G5) (4).

PROTEINURIA: Dipstick '2+' of proteinuria or urine protein: creatinine ratio of ≥ 0.02 g/mmol (4).

STAGING OF CKD

GFR categories in CKD (ml/min/1.73 m²) (4)

CKD 3	30 – 59	Moderately decreased
CKD 4	15 – 29	Severely decreased
CKD 5	<15	Kidney failure

METABOLIC ACIDOSIS

Serum bicarbonate concentrations <22 mmol/l (4).

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)

Is according to the original Schwartz formula where creatinine was measured using kinetic Jaffe methods where $k \sim 0.33$ (preterm infant), $k \sim 0.45$ (full term), $k \sim 0.55$ (children and adolescent females), $k \sim 0.7$ (adolescent males). Modified Schwartz formula where creatinine was measured using enzymatic methods, $k \sim 0.413$ (46).

$$eGFR = \frac{k * L(cm)}{creat(umol/l)}$$

MINERAL AND BONE DISEASE (MBD)

Abnormal vitamin D (low plasma 25 (OH)D and low 1,24(OH)₂D), low calcium, high phosphate, and increased parathyroid hormone (PTH) and X-ray changes of renal osteodystrophy (48).

HYPOALBUMINEMIA

Serum albumin <25g/L (40).

KIDNEY SUPPORTIVE CARE

An approach that aims to improve the quality of life for people for whom kidney disease, either directly or indirectly, substantially impacts their well-being, treatment options, or access to care, and their families, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual (*Conservative kidney management and kidney supportive care: core components of integrated care for people with kidney failure*) (43).

CONSERVATIVE KIDNEY MANAGEMENT

Care for people with kidney failure that focuses predominantly on providing KSC to promote quality of life but does not include KRT (*Conservative kidney management and kidney supportive care: core components of integrated care for people with kidney failure*) (43).

APPENDIX D: DATASHEET

DATABASE						
Patient Code						
Date of initial presentation						
Date of final outcome						
Outside hospital referral						
	North West Province					
	Thelle Mogoerane Hospital					
	Sebokeng Hospital					
DEMOGRAPHIC VARIABLES						
Age at presentation						
	2 to <5 yr.					
	5 to < 10 yr.					
	10 to 14 yr.					
Gender						
	Female					
	Male					
Race						
	Black-African					
	White					
	Mixed Race					
	Indian/Asian					
PATIENT VARIABLES						
Initial weight (kg) at presentation						
Initial length/height (cm)						
KIDNEY FUNCTION			5yrs	10yrs	15yrs	20yrs
Creatinine (umol/L)	At presentation					
eGFR (ml/min/1.73m ²)	At presentation					
CKD stage	At presentation					
3 (GFR 30–59mL/ min/1.73m ²)						
4 (GFR 15– 29 mL/min/1.73m ²)						
5 (GFR <15mL/min/1.73m ²) or dialysis						
Dipstick						
	Proteinuria					
	Haematuria					
	Glucosuria					
	Leucocytes					

AETIOLOGY					
Glomerular Causes					
Primary causes					
Nephrotic Syndrome					
	Yes				
		SSNS			
		SRNS			
		SDNS			
	No				
Glomerulonephritis					
	Yes				
		Membranous glomerulonephritis			
		IgA nephropathy			
		Membranoproliferative glomerulonephritis (MPGN)			
		Crescentic glomerulonephritis			
		Other			
Secondary causes					
	Yes				
		Lupus nephritis			
		HSP Nephritis			
		ANCA associated vasculitis			
		Post-infectious glomerulonephritis			
		HIV nephropathy			
		Syphilis			
		Hepatitis B			
		Malignancy			
		Other			
	No				
CAKUT					
	Yes				
		Renal agenesis			
		Renal atrophy/hypoplasia/dysplasia			
		Reflux nephropathy (VUR)			
		Pelviureteric junction (PUJ)			
		Vesicoureteric junction (VUJ)			
		Posterior urethral valves (PUV)			
		Ureterocoele			
		Crossed renal ectopia			

		Duplex kidney				
		Horseshoe kidney				
		PBS				
		Megaureter				
		MCDK				
		ADPKD				
		ARPKD				
	No					
Voiding disorders						
	Yes					
		Non-neurogenic neurogenic bladder (Hinman syndrome)				
		Neuropathic bladder				
	No					
Other						
	Cystinosis					
	Oxalosis					
	AKI					
RISK FACTORS						
Family history						
	Yes					
	No					
Neonatal factors						
Premature (<37)						
LBW (1500g to <2500g)						
Neonatal AKI						
Abnormal ante-natal sonar						
COMPLICATIONS						
Initial visit blood results and imaging			5yrs	10yrs	15yrs	20yrs
Haemoglobin (g/dL)						
MCV (fL)						
RCDW (%)						
Ferritin (ng/ml)						
Iron supplements						
Hypertension						
	ACE-I					
	ARB					
	CCB					
	B-blocker					
	Diuretic					
	Alpha-blocker					
Echocardiography						
	LVH					

	DCMO					
	Vascular calcification					
Albumin (g/L)						
Mineral Bone disease						
	Yes					
	No					
Carbon dioxide (mmol/L)						
TSH (mIU/L)						
Total cholesterol (mmol/L)						
OUTCOME	Initial date	5yrs	10yrs	15yrs	20yrs	
Conservative						
Peritoneal dialysis						
Haemodialysis						
CRRT						
Kidney transplantation	Referral					
Death						
Lost to follow up						
Transfer out						

APPENDIX E: TURNITIN REPORT

Draft Manuscript_NAN18.03.2025.do CX

by Karen Petersen

Submission date: 18-Mar-2025 08:25PM (UTC+0200)

Submission ID: 2618383842

File name: Draft_Manuscript_NAN18.03.2025.docx (310.03K)

Word count: 13069

**A DESCRIPTIVE STUDY OF CHRONIC KIDNEY DISEASE
(STAGES 3-5) IN CHILDREN AT CHRIS HANI
BARAGWANATH ACADEMIC HOSPITAL, 2000-2019**

by

Nokukhanya Ngubane-Mwandla,
(1332856)

Co-authors: Shannon Leahy, Nilesh Lala, Zvifadzo Matsena-Zingoni, Karen L Petersen

Supervisors:

Prof. Karen L Petersen

Dr. Nilesh Lala

A Dissertation submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of
Master of Science in Medicine (MSc).

Johannesburg, 2025.

ABSTRACT

Background

The epidemiology and outcome of chronic kidney disease (CKD) in children of less resourced countries are largely underreported because of paucity of data systems.

Methods

A retrospective follow-up study of children aged 2 to 14 years with CKD stage 3 to 5 at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa, from 2000-2019.

Results

A total of 198 children were analysed. Sixty-five (32.8%), 47 (23.7%), and 86 (43.4%) had CKD stages 3, 4 and 5 at diagnosis, respectively. The median (inter quartile range (IQR)) age at diagnosis was 7 (4-11) years and duration of follow up was 1.2 (0.3-3.2) years. The calculated annual incidence in 2001 to 2019 ranged from 9.3 to 29.7 per million age related population (PMARP). Glomerular disease accounted for 74 (37%); congenital anomalies of the kidney and urinary tract (CAKUT) for 64 (32%).

At final outcome, 108 children had CKD stage 5. Seventy-three (67.5%) received kidney replacement therapy (KRT) and 35 (32.4%) treated conservatively. The mean rate of decline in eGFR from baseline to final visit was 4.90 (SD 7.03) ml/min/BSA per year. The mortality rate was 9.8% (7.3 to 13.1%) person-years (PY), contributed by 46 (23.3%) children. The two-year survival for glomerular disease was 50% compared to 90% for CAKUT. Risk of mortality increased in CKD stage 5 (AHR=3.5; 95%CI:1.5-7.9, p-value 0.002), hypoalbuminemia (AHR=2.6; 95%CI:1.0-6.2, p-value 0.030) and glomerular disease (AHR=2.5; 95%CI:1.0-6.3, p-value 0.046).

Conclusion

This cohort presented in advanced CKD. Barriers to access renal services should be addressed to achieve sustainable developmental goals (SDG).

Keywords: Chronic kidney disease, low- and middle-income countries, Sustainable developmental goals, kidney replacement therapy, non-communicable disease, conservative

kidney management, Incidence per million age-related population, Children, South Africa, Glomerular disease.

Word count: 247

CHAPTER ONE – INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

South Africa, an upper middle-income country (UMIC) is moving towards sustainable developmental goals (SDG) which includes reducing premature mortality from non-communicable diseases by a third by year 2030 (1). Chronic kidney disease (CKD) is one of the silent causes of mortality in the adults and paediatric population. It is said to become the 5th leading cause of mortality by year 2040 (2). With the decreasing number of kidney transplantations occurring in low resource settings (3), it becomes essential to report on the epidemiology, risk factors, spectrum of diseases and outcomes of children with CKD, especially moderate to severe CKD i.e., CKD stages 3 to 5.

The Kidney Disease Improving Global Outcomes (KDIGO) provides evidence-based clinical guidelines on the management of kidney diseases. It defined CKD as abnormalities of kidney structure or function that is present for greater than three months (4). Chronic kidney disease is further classified into different stages of severity based on the estimated glomerular filtration rate (eGFR) and albuminuria category (4). The most severe form of CKD is kidney failure (KF), also known as end stage kidney disease (ESKD) or CKD stage 5 (5). It is defined as an eGFR less than 15ml/min/1.73m² or the need for dialysis (5). Dialysis therapy and or kidney transplantation are components of kidney replacement therapy (KRT) to substitute life-sustaining kidney function (6). The latest South African Renal Registry (SARR) reports on 849 patients starting KRT in the year 2021, majority of which (80%) treated in the private sector. This provided an incidence of 14.1 per million population (pmp). Most of the population in South Africa (85.4%) rely on public healthcare facilities and only a small proportion (14.6%) with medical insurance access private healthcare (7). Measures to equalise these disparities are needed.

Africa is burdened with communicable and non-communicable diseases, in addition to socio-economic challenges (1, 8). This shapes the unique patterns of aetiologies, risk factors and outcomes of children with CKD. Chronic kidney disease can be asymptomatic until it progresses to advanced stages, leading to underestimates of incidence and prevalence (9). Delayed CKD diagnosis can lead to preventable morbidity and increased health care costs

(9). There is a pressing need for early identification and prevention strategies (10). Improved health care systems and adequate resource allocation for patients with CKD is proposed. (8). More than half of the children in the world less than 15 years of age reside in less resourced countries (11). This study aimed to describe the epidemiology, demographic characteristics, aetiology and risk factors of children, 2 to 14 years, diagnosed with moderate to severe CKD over two decades; as well as analyse the complications, treatment and outcomes. This is a single centre study in a Tertiary Hospital in Soweto, South Africa, Chris Hani Baragwanath Academic Hospital (CHBAH). The hospital provides tertiary services to surrounding regions within and outside of Gauteng province.

1.2. LITERATURE REVIEW

1.2.1. DEFINITION

Kidney diseases play a significant role in the cause of morbidity and mortality worldwide, with an increasing prevalence globally (12). The global annual mortality due to chronic kidney disease (CKD) is predicted to be 2.2 million in 2040, up by 1 million from year 2017 (8). Early stages of chronic kidney disease in children are often under diagnosed and under reported as it is frequently asymptomatic (13). It is advantageous to diagnose CKD in early stages so timely treatment can be implemented to preserve residual renal function.

Although widely adopted, the KDIGO guideline is criticized for its limited applicability. The criteria for eGFR below 60ml/min/1.73m² are inapplicable to children less than two years of age, since in the newborn period the eGFR is significantly less than 60ml/min/1.73m², and increases rapidly reaching normal adult values by 2 years of age (4, 14). Therefore, normal maximal values for eGFR for this age group will naturally be less than those of an older child or adult (4). In addition, children born with clinically severe congenital abnormalities of the kidney and the urinary tract (CAKUT) are flagged to have CKD before awaiting three months for this diagnosis (13). Various formulae are available to determine eGFR; however, the Schwartz formula is the most widely utilised in children (13, 15).

1.2.2. EPIDEMIOLOGY

There is little information on the epidemiology of chronic kidney disease in children, especially in less resourced countries (13). In high income countries such as Europe, the

incidence of CKD stages 3-5 in children is 11-12 per million of the age-related population (pmarp) (13). In the United States and Canada, the incidence of kidney failure in children 0-19 years of age is 9-16 pmarp (13). Gender and race also play a pivotal role in the incidence of CKD. It is higher in males because of greater occurrence of CAKUT in this gender (13). In North America, Australia and New Zealand there is a higher incidence of CKD and kidney failure in African-American and indigenous children compared to the rest of the paediatric population (13). This could be attributed to genetic predisposition and to the social determinants of health.

In Africa the incidence of CKD is mostly unknown due to scarce data systems. (16). The incidence of CKD in sub-Saharan Africa is thought to be higher than is known (17). The limited studies on childhood kidney failure in sub-Saharan Africa are primarily from Nigeria and South Africa (18). These single-centre studies report an incidence of CKD in children below age of 16 years to be 3 pmarp in Nigeria and 1-2 pmarp in South Africa (13). Reasons for the low incidence could be due to short study period, lack of national renal registries documenting all stages of CKD and missed diagnosis.

South Africa (SA) although an upper middle-income country (UMIC), has the highest Gini coefficient (0.63) globally, reflecting significant wealth disparities (19). Gauteng, a small yet most urbanised province, comprises the largest share of South Africa's population. The median age in South Africa is 27.6 years in year 2021 (20). It is challenging to perform large scale epidemiology studies in SA because of the limited renal services in some provinces. A recent adult study in a tertiary hospital in Bloemfontein report an average annual ESKD incidence of 49.9 (95 %confidence interval [CI], 35.8-64.0) per-million-population (21). A study done in Kwa-Zulu Natal, South Africa on children less than 16 years of age with CKD stages 2 to 5 identified 89 (68.2%) children with CKD stage 3 to 5 over their 11-year study period (16). In the 2022 South African Renal Registry (SARR), there were 822 adult patients who started KRT, an incidence of 13.3 per million population (pmp) (7). The SARR reports only on patients in CKD stage 5 who receives kidney replacement therapy which limits the calculation of CKD incidence. In the private health sector in SA, the number of Discovery Health Medical Scheme (DHMS) members who are registered as having CKD exponentially increased from 2008 to 2022, i.e. a 4.6-fold increase in incidence (22). This may be due to longer life expectancy. The incidence of CKD in children residing in Gauteng is currently unknown.

Although the diagnosis of CKD increases with advancing age, young adults in Sub-Saharan Africa (SSA) are highly affected due to greater incidences of chronic glomerulonephritis, alternative herbal medication, and communicable diseases (21). This is compounded by the limited number of nephrologists, especially paediatric nephrologists (23). Other contributing factors include limited resources, poor access to kidney replacement therapy, and high prevalence of poverty (23). It is proposed a national registry in SA, like the SARR, for children with CKD stage 3 to 5 be developed. It will provide vital information on the epidemiology of CKD in children in SA and help identify risk factors for progression of kidney disease (17).

1.2.3. RISK FACTORS

Besides genetic factors, low- and middle-income (LMIC) countries face the challenge of CKD encouraged by infections, prematurity and low birth weight (24). In addition, socio-economic influences such as inadequate sanitation, pollution, malnutrition and traditional medicine propel CKD (24). Another major contributor to the burden of CKD is acute kidney injury (AKI) due to hypovolemia and septic shock complications and is associated with high mortality and progression to CKD (14, 24).

Infectious diseases in LMIC contributing to a greater incidence CKD include tuberculosis, hepatitis, schistosomiasis, post-infectious glomerulonephritis and human immunodeficiency virus (HIV) associated nephropathies (17, 24). At Chris Hani Baragwanath Academic Hospital (CHBAH) between 1990 and 2012, acute post infectious glomerulonephritis was the most common cause of crescentic glomerulonephritis, a risk factor for CKD (25). In a ten-year review study at the Red Cross Children's Hospital, 75% of children with crescentic glomerulonephritis on one year of follow up either developed CKD, needed chronic dialysis or a kidney transplant (26).

1.2.4. AETIOLOGY

Data from renal registries in high income countries show that in children, CAKUT predominate over glomerular disease (12). Studies from LMIC in Africa, Asia, Middle East and South American all show glomerular disease is the main cause of paediatric kidney disease, in contrast to high income countries (12). The reason for the difference is allegedly due to more exposure to immune-stimulating antigens associated with glomerulonephritis in the LMIC (17). In addition, in LMIC, the proportion of CKD due to CAKUT is determined

by the availability of antenatal sonars, mortality in infancy, and the progression to kidney failure after childhood (27).

The two frequent causes of kidney failure in children of South Africa are glomerular disease (83%) followed by CAKUT (8.5%) for the year of 2012 (17). Glomerular disease occurs mainly in children older than 10 years while CAKUT predominates in younger children (13,18). The causes of glomerular disease vary among different continents in Africa, ranging from parasites like bilharzia to malaria, hepatitis B, syphilis, HIV and other infections (12, 28, 29). Focal segmental glomerular sclerosis is increasing across all racial groups in South Africa (30). It is one of the classic causes of steroid resistant nephrotic syndrome (SRNS) (30). Steroid resistant nephrotic syndrome is one of top three causes of end stage kidney disease (ESKD) in the 2006 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) on children who were transplanted. (31).

Of the CAKUT conditions, posterior urethral valves (PUV) are a common cause of congenital obstructive uropathy and can lead to CKD (32). At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), 44.8% of children with CAKUT had posterior urethral valves (PUV) (33). At CHBAH, 34.8% of patients with PUV present with CKD at the final follow up visit (34).

Metabolic and genetic diseases such as renal tubular acidosis, cystinosis, and oxalosis are rare diseases with high risk of progression to CKD (29). Local data for children at CHBAH with primary hyperoxaluria and CKD reports a mortality rate of 78.9% (35).

1.2.5. COMPLICATIONS

Chronic kidney disease is a pro-inflammatory condition with multisystem effects (36). A SA study in 2017, reports modifiable cardiovascular risk factors such as increased total cholesterol and decreased albumin levels are associated with mortality (37). More aggressive treatment of blood pressure, hyperphosphatemia, acidosis and dyslipidaemia may slow the progression of CKD as well as decrease cardiovascular disease (CVD) (38). Other important complications include stunting and anaemia (38). Anaemia is associated with high morbidity and mortality in children with CKD (39). A SA study in 2018 reports serum ferritin levels and red cell distribution width to be independent predictors of anaemia with or without iron deficiency in children with CKD (39). A study in a tertiary hospital in India identifies

anaemia, hypocalcaemia, short stature and hyperparathyroidism significantly correlating with severity of CKD in children (40).

1.2.6. TREATMENT

Children with kidney failure have the following four treatment options: pre-emptive kidney transplantation, peritoneal dialysis (PD), haemodialysis (HD) and conservative kidney management without dialysis. In SA, UK and most other European countries PD is the first treatment of choice (41). In the 2012 SARR, the most common mode of KRT for children was peritoneal dialysis (61%) compared to haemodialysis (39%) (17). In contrast over seventy percent of adult patients in SA received HD while 18% received PD and 10.6% received a kidney transplant in 2018 (42). Three paediatric dialysis units in Gauteng province (CHBAH, CMJAH, private hospital) treated 75% of South Africa's children in 2012 (17). Dialysis in the private sector is equivalent to the best dialysis centres in the world, however, dialysis in public sector lags due to various reasons including high costs (43).

Treatment requires skilled medical and nursing staff. Unfortunately, Africa experiences a shortage and instability of skilled healthcare workers. In addition, migration of healthcare workers has a great impact on public healthcare systems and delivery, especially affecting India, Nigeria, Pakistan, and South Africa countries where most migration takes place (44). Training of allied healthcare workers such as nurses, pharmacists, and community healthcare workers, can provide a solution by taking on uncomplicated tasks (such as urinalysis) in multidisciplinary clinics, hypertension centres, and patient triage. However, for this to be effective, training modules and protocols of disease diagnosis, treatment and referral will need to be in place. (44).

Transplantation tends to be more cost effective compared to dialysis and produces better quality of life (43). For most LMIC, transplantation is limited by resources, including low numbers of registered organ donors (only 0.2% in South Africans) and survival is adversely affected by the affordability of immunosuppressive drugs, malnutrition and infectious disease (43). Sub-Saharan Africa still falls into the lowest quartile of transplantation rates worldwide (23) and in SA, transplant centres are currently limited to a few major cities (23).

There is a national KRT rationing policy in place for patients in the public sector incorporating criteria that selects patients considered to benefit the most from transplantation to balance the growing need for KRT in a resource constrained environment (21).

Conservative kidney management (CKM) is a treatment option for families who choose not to undertake KRT (44). Effective CKM and KSC (kidney supportive care) programs are needed in both high and low resource settings. Conservative kidney management and KSC are core components of integrated kidney care (45). A recent local study in Cape Town has developed a tool kit [Paediatric Feasibility Assessment for Transplantation (pFAT)], a psychosocial risk score developed in South Africa to support transparent eligibility assessment in a low-resource setting (46). It highlights the need to address specific psychosocial and socioeconomic barriers, to encourage equitable access to KRT. Equally important, is the need for strategies to delay CKD progression (46).

1.2.7. OUTCOME

The mortality rate in children on KRT is approximately thirtyfold greater than their healthy counterparts (13). The major causes are cardiovascular diseases and infections, contributing 30-40% and 20-50% of deaths respectively (13). Infection is now the commonest cause of hospital admissions compared to acute rejection for children who received a kidney transplant (13).

This study aimed to address the research gap in the epidemiology, aetiology, risk factors, and outcomes of children with moderate to severe CKD in a SA setting.

1.3. AIMS AND OBJECTIVES

1.3.1. AIMS

This study aim was to describe the epidemiology, and characteristics of patients with an initial diagnosis of CKD stage 3 to 5 at the paediatric renal unit at CHBAH. The study also aimed to analyse the aetiology and risk factors associated with poor outcome i.e., end-stage kidney disease (ESKD) or death.

1.3.2. OBJECTIVES

1.3.2.1 To determine the frequency of kidney failure (CKD stage 5 or initiation of kidney replacement therapy) in children diagnosed with moderate to severe CKD at CHBAH paediatric renal unit between 01st January 2000 and 31st December 2019.

1.3.2.2 To describe the demographic characteristics, aetiology and risk factors of children with CKD stage 3 to 5.

1.3.2.3 To analyse complications, treatment and outcomes of children with CKD stage 3 to 5.

CHAPTER TWO – METHODS AND MATERIALS

2.1. STUDY DESIGN AND SITE

This was a retrospective observational study of children with CKD stage 3 to 5, treated at the Paediatric Renal Unit of Chris Hani Baragwanath Academic Hospital (CHBAH) from 01 January 2000 to 31 December 2019. Archived patient records were retrieved to identify patients.

Chris Hani Baragwanath Academic Hospital (CHBAH) also known casually as “Bara” is the largest hospital in South Africa and Africa. Its size (0.70 km²) and bed capacity (3200 beds and 429 buildings) places CHBAH among the top ten largest hospitals in the world (47).

The hospital is located in Soweto, Johannesburg. Chris Hani Baragwanath Academic Hospital is a teaching hospital affiliated to the University of the Witwatersrand Medical School, along with three other nearby teaching hospitals. In addition to being a tertiary referral hospital for much of Gauteng province (11.4 million), North West province (3.7 million), parts of the Northern Cape, and informally the rest of South Africa, except the Western Cape (47), it also provides service to its immediate population of at least 1.5 million adults and children in the surrounding Soweto (47). In Johannesburg, CHBAH is a tertiary academic referral hospital serving regions D, F, and G, see figure 1. It has a total of 408 paediatric beds. The Paediatric Renal Unit at CHBAH consults up to 400 inpatients and 1500 outpatient visits annually. The unit offers acute and chronic PD as well as acute HD. Patients requiring chronic HD and transplantation are referred for quaternary services at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), since year March 1969 also to Nelson Mandela Children’s Hospital (NMCH) since June 2021. Continuous renal replacement therapy (CRRT) is offered in PICU by the Intensivists at CHBAH. See figure 2.1 below.



Figure 2. 1 Johannesburg regions. Available from: <https://www.commonwealthofnations.org/partner/city-of-johannesburg-metropolitan-municipality/>

2.2. STUDY POPULATION

The paediatric renal unit provides services to patients admitted to the neonatal unit, general paediatric wards, paediatric oncology unit, paediatric surgical disciplines including the burns unit, and the paediatric Intensive Care Unit. This study population included patients from two years to 14 years of age who consulted at the paediatric renal unit at CHBAH during the study period.

These patients were categorised into three groups based on the eGFR: CKD stage 3 (eGFR 59 – 30 mL/min/1.73m²), CKD stage 4 (eGFR 29 – 15 mL/min/1.73m²) and CKD stage 5 (eGFR less than 15 mL/min/1.73m² or initiation of dialysis) at diagnosis (4).

The following flow chart (Figure 2.2) shows how the children were sampled and included in the study:

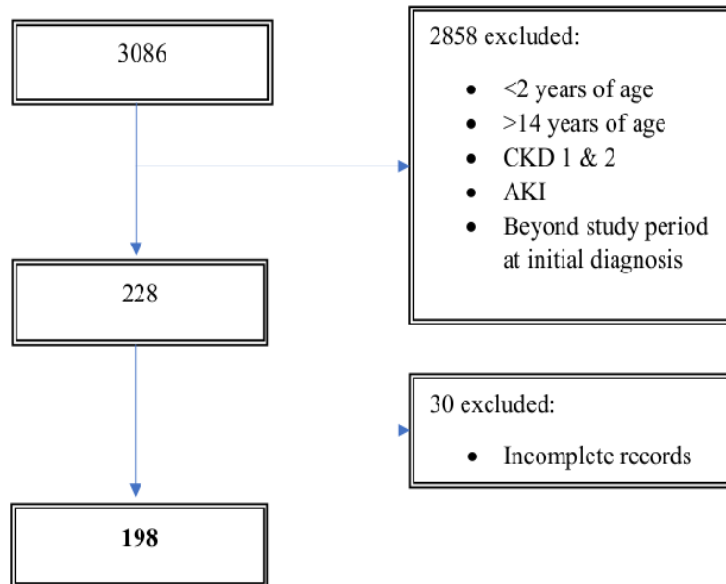


Figure 2. 2 Flow chart of inclusion criteria of the study population.

2.2.1. Data sources

Data was collected from patient clinical records stored in the renal unit. The study variables included demographics and clinical variables. Kidney function was assessed by estimation of the GFR (eGFR) using the modified Schwartz formula (48) for categorisation of CKD stages.

The aetiology was grouped into glomerular causes and non-glomerular causes. Risk factors included a family history of renal disease and neonatal factors such as prematurity, low birth weight and AKI. Complications were assessed by recording of initial consult results for presence of cardiovascular disease, anaemia, hypothyroidism, mineral and bone disease, metabolic acidosis, hypoalbuminemia and dyslipidaemia.

Management was grouped into conservative management and kidney replacement therapy. Children outcome to survival or death was recorded and analysed. Transfer out to another renal facility during the study period was counted as survivors. Patients who have not adhered to scheduled visits were recorded as lost to follow-up. Refer to definitions and database appendices for all the variables.

2.2.2. Outcome measurement

Outcome variables included active patient, transfer to another renal facility, lost to follow-up, or death.

Treatment variables included PD, HD, or CKM.

2.2.3. Study time

Data was collected for the 20-year period from January 2000 to December 2019. Analysis was performed from initial diagnosis of CKD stage 3, 4 or 5 to final outcome or end of the study period in December 2019, whichever came first.

2.3. DATA ANALYSIS

Data was managed using STATA version 17 (49).

Annual Incidence rates Per Million Age Related Population (PMARP) was calculated using the formula:

$$\text{New CKD 3 to 5 minus cases outside Gauteng for year} \times 1\text{million} \div \text{population indices for children aged 2 to 14 years for the same year.}$$
It was calculated for each year and reported as a range for the year 2001 to 2019.

The population indices were supplied by the District Health Information System (DHIS), which are obtained from the STATS_SA database.

Categorical variables were summarised using frequencies and percentages. Laboratory variables were categorised based on the recommended clinical threshold values for normal range. Continuous variables were assessed for normality using the Shapiro Wilk test and the histogram plots with a superimposed normal curve. Since all the variables deviated from the normal distribution, the median and interquartile range (IQR) were used as the measures of central tendency. The Kruskal Wallis test was used to test the significance difference of laboratory findings between the CKD stages. To determine the factors associated with mortality among CKD patients, the Cox proportional hazard model was used. Kaplan and Meier curves were used to describe the mortality rates between groups of categorical variables. The

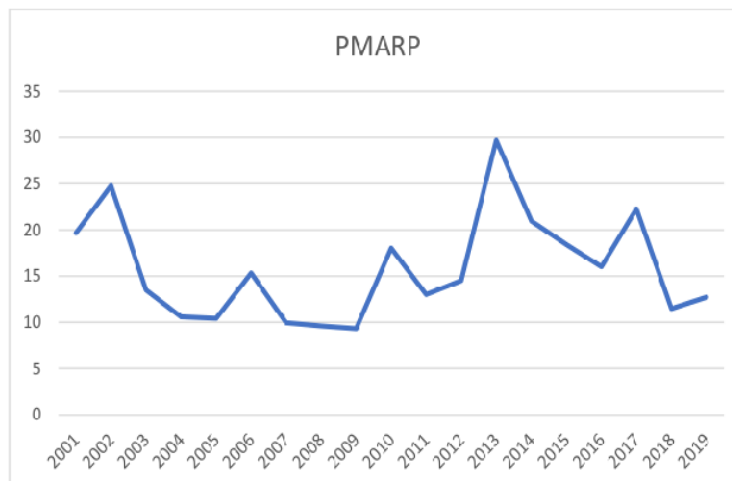
univariate and multiple Cox regression models were fitted. The proportional hazard assumption was assessed using the Scholefield residual test. Significance was set at 5%.

2.4. ETHICS

The study protocol was accepted by the University of the Witwatersrand Human Research Ethics Committee, certificate number M210468 and approved by CHBAH Paediatric department as well as the Medical Advisory Committee (MAC). The study was registered in the National Health Research Database (NHRD). The research was performed in line with the principles of the Declaration of Helsinki. Informed consent was not required due to the study being retrospective. Each patient had a study number to ensure anonymity.

CHAPTER THREE – RESULTS

A total of 65 (32.8%), 47 (23.7%), and 86 (43.4%) patients had CKD stages 3, 4 and 5 respectively. The calculated incidence for 2001 to 2019 ranged from 9.3 to 29.7 PMARP as seen in figure 3.1.



*The denominator for year 2000 could not be supplied by DHIS.

Figure 3. 1 PMARP per year

3.1. BASELINE CHARACTERISTICS AT DIAGNOSIS

Table 3.1 shows the baseline characteristics of the participants at diagnosis. The overall median (IQR) age at initial diagnosis of CKD stage 3 to 5 was 7 (4-11) years. Of the 41 (20.7%) who resided outside Gauteng Province, 21 (51.2%) presented in CKD stage 5, compared to 65 of 157 (41.4%) who resided in Gauteng.

Table 3. 1 Baseline characteristics at diagnosis

	CKD stage 3 n = 65 (32.8%)	CKD stage 4 n = 47 (23.7%)	CKD stage 5 n = 86 (43.4%)	Total n=198
Age (years)				
Median (IQR)	7 (4 -10)	6 (3 -10)	7 (5 -11)	7 (4-11)
Weight (z-score)				
Median (IQR)	-1.3 (-3.0 to 0.4)	-1.8 (-2.7 to -1.0)	-1.6 (-2.9 to -0.4)	-1.6 (-2.8 to -0.4)
Height (z-score)				
Median (IQR)	-1.5 (-3.1 to -0.3)	-1.9 (-3.4 to -1.1)	-1.6 (-2.7 to -0.4)	-1.7 (-3.0 to -0.5)
Province,				
Outside Gauteng, n (%)	11 (16.9)	9 (19.1)	21 (24.4)	41 (20.7)
Inside Gauteng, n (%)	54 (83.0)	38 (80.8)	65 (75.5)	157 (79.2)
Gender				
Male, n (%)	28 (14.1)	33 (16.6)	45 (22.7)	106 (53.5)
Female, n (%)	37 (56.9)	14 (29.7)	41 (47.6)	92 (46.4)

Table 3.2 shows the aetiology of the CKD stages 3, 4 and 5 by age groups. Glomerular disease was the predominant cause of CKD in patients older than 5 years in 61 (43.5%). Overall, of the glomerular diseases nephrotic syndrome accounted for 35 (17.6%); 32 (91.4%) steroid resistant nephrotic syndrome (SRNS), two (5.7%) steroid sensitive nephrotic syndrome (SSNS) and one (2.8%) steroid dependent nephrotic syndrome (SDNS). The histological types were focal segmental glomerulosclerosis (FSGS) in 19 (54.2%), minimal change nephrotic syndrome (MCNS) in four (11.4%), congenital nephrotic in six (17.1%), and unknown in six (17.1%). HIVAN accounted for 22 (11.1%); two (9.0%) before year 2004 and 20 (90.9%) after year 2004 when anti-retroviral (ARV) treatment became available (23).

The predominant cause in the 2-to-5-year age group was CAKUT in 25 (43.1%); posterior urethral valves (PUV) accounted for 28 (14.1%) overall.

Table 3. 2 Aetiology of CKD 3 to 5 by age groups

Age groups	2- 5yrs n (%)	≥5yrs n (%)	Total n (%)
Total	58 (29.3)	140 (70.7)	198 (100)
Glomerular disease	13 (22.4)	61 (43.5)	74 (37.3)
Nephrotic syndrome	10 (5.0)	25 (12.6)	35 (17.6)
HIV-Related Kidney Disease	2 (1.0)	20 (10.0)	22 (11.1)
^a Other	-----	12 (6.0)	12 (6.0)
Lupus nephritis	-----	4 (2.0)	4 (2.0)
APIGN	1(0.5)	-----	1 (0.5)
CAKUT	25 (43.1)	39 (27.8)	64 (32.3)
Posterior urethral valves	17 (8.5)	11 (5.0)	28 (14.1)
^b Other CAKUT	6 (3.0)	16 (8.0)	22 (11.0)
^c Other obstructive uropathy	1 (0.5)	7 (3.5)	8 (4.0)
Prune Belly Syndrome	1 (0.5)	5 (2.5)	6 (3.0)
Genetic Syndromes	9 (15.5)	14 (10.0)	23 (11.6)
Primary hyperoxaluria	5 (2.5)	11 (5.5)	16 (8.0)
Syndromic	1 (0.5)	2 (1.0)	3 (1.5)
ARPKD	2 (1.0)	-----	2 (1.0)
Cystinosis	-----	1 (0.5)	1 (0.5)
Nephronophthisis	1 (0.5)	-----	1 (0.5)
Voiding disorders	4 (6.8)	13 (9.2)	17 (8.5)
Neurogenic bladder	4 (2.0)	11 (5.0)	15 (7.5)
Dysenergetic bladder	-----	2 (1.0)	2 (1.0)
Acute kidney injury	5 (8.6)	4 (2.8)	9 (4.5)
CKD cause unknown	1 (1.7)	5 (3.5)	6 (3.0)
Vasculitis	-----	3 (2.1)	3 (1.5)
Primary hypertension	-----	1 (0.7)	1 (0.5)
Pyelonephritis	1 (1.7)	-----	1 (0.5)

HIV-Related Kidney Disease includes HIVAN (HIV nephropathy) (21.10.6%) and HIVIC (HIV-Associated immune complex kidney disease) (1, 0.5 %); APIGN (Acute post-infectious glomerulonephritis); CAKUT (Congenital abnormalities of the kidney and urinary tract); ARPKD (autosomal recessive polycystic kidney disease);

^aOther glomerular disease included the following: Immune complex glomerulonephritis (4.2%), tubulointerstitial nephritis (3.1.5%), membranoproliferative glomerular nephritis (2.1.0%), granulomatosis with polyangiitis (2.1.0%), IgA nephropathy (1.0.5%).

^bOther CAKUT included: dilated non-obstructed system (1.0.5%), horseshoe kidney (2.1.0%), multicystic dysplastic kidney (2.1.0%), hypoplastic dysplastic kidneys (2.1.0%), pelvic ureteric junction obstruction (3.1.5%), ureter stricture (2.1.0%), vesicoureteral reflux (6.3.0%), unilateral renal agenesis (4.2.0%).

^cOther obstructive uropathies included: urethral obstruction (1.0.5%), posterior urethra diverticulum (1.0.5%), megalourethra (1.0.5%), rhabdomyosarcoma (1.0.5%).

3.2. RISK FACTORS AT DIAGNOSIS

Risk factors for CKD were identified in 35 (17.6%) patients at diagnosis. In the 35 patients, low birth weight and prematurity was reported in 14 (40%), nine (25.7%) had antenatal hydronephrosis, seven (20%) had a positive family history of renal disease, two (5.7%) had AKI and three (8.5%) had other diagnosis which included small for gestational age (2, 5.7%) and birth asphyxia (1, 2.8%), see figure 3.2.

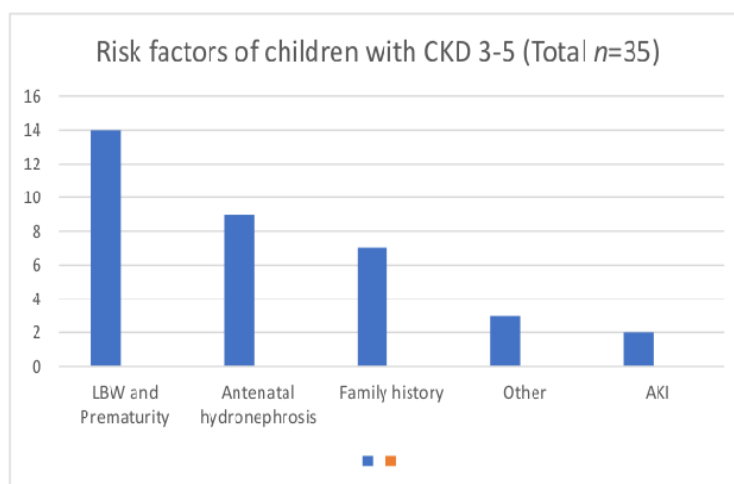


Figure 3. 2 Risk factors of children with CKD stage 3 to 5

3.3. COMPLICATIONS AT DIAGNOSIS

At diagnosis, 111 (56.0%) patients had hypertension. Hypertensive heart disease was documented in 63 (31.8%) on echocardiogram. No vascular calcifications were documented.

Table 3.3 shows the laboratory blood results at diagnosis. Haemoglobin, bicarbonate, and calcium were significantly lower in CKD stage 5 compared to CKD stage 3 and 4 at presentation, while serum phosphate, PTH and ferritin were significantly higher.

Table 3. 3 Laboratory results at diagnosis.

Variable	CKD stage 3	CKD stage 4	CKD stage 5	p-Value
	Median (IQR)	Median (IQR)	Median (IQR)	
Haemoglobin (g/dL)	11 (9.3 to 12.6)	10.4 (8.95 to 11.32)	8 (6.3 to 9.7)	0.0001
^a MCV (fL)	81.1 (75.9 to 85.6)	79.7 (76.6 to 83.5)	78.9 (73.9 to 82.8)	0.1179
Ferritin (ng/mL)	44 (22 to 184)	83 (46 to 293)	338 (152 to 671)	0.0001
Albumin (g/L)	32 (18 to 43)	38 (23 to 43)	29 (23 to 37)	0.1553
Bicarbonate (mmol/L)	16 (14 to 20)	13 (11 to 17)	11 (6 to 14)	0.0001
^b TSH (mIU/L)	3.7 (2.26 to 9.5)	4.44 (2.73 to 6.43)	4.38 (2.58 to 6.54)	0.9870
^c TC (mmol/L)	8.65 (6.49 to 12.4)	8.26 (4.2 to 9.41)	5.2 (3.79 to 7)	0.0004
Calcium (mmol/L)	2.28 (2.04 to 2.39)	2.3 (2.08 to 2.5)	2 (1.55 to 2.28)	0.0001
Magnesium (mmol/L)	0.85 (0.77 to 0.99)	0.93 (0.83 to 1.1)	0.94 (0.8 to 1.08)	0.2618
Phosphate (mmol/L)	1.70 (1.45 to 1.98)	1.67 (1.48 to 2.16)	2.23 (1.71 to 2.87)	0.0001
^d PTH (pmol/L)	10.25 (7.1 to 10.8)	17.1 (9.8 to 25)	45.1 (20 to 67.9)	0.0008

^aMean corpuscular volume, ^bThyroid stimulating hormone, ^cTotal cholesterol, ^dparathyroid hormone.

3.4. KIDNEY FAILURE TREATMENT OUTCOME

Patients with CKD can progress or improve from one CKD stage to another. With medical treatment the rates of progression may differ among institutions. Of the 86 children with CKD stage 5 at initial diagnosis, 79 (91.8%) remained in CKD stage 5 at final outcome. Likewise, of the 65 children with CKD stage 3 at initial diagnosis, 14 (21.5%) progressed to CKD stage 5. Forty-seven children had initial CKD stage 4, of those 15 (31.9%) progressed to CKD stage 5. This resulted in a total of 108 children with CKD stage 5 at final outcome as seen in Table 3.4.

Table 3. 4 Progression of CKD from initial stage at diagnosis to CKD stage at final outcome.

CKD stage at initial diagnosis	CKD stage at final outcome				Total rows
	CKD 2	CKD 3	CKD 4	CKD 5	
CKD 3	0	39	12	14	65
CKD 4	1	2	29	15	47
CKD 5	1	3	3	79	86
Total column	2	44	44	108	198

The mean rate of decline in eGFR from baseline to final visit was 4.90 (SD 7.03) ml/min/BSA per year.

A total of 198 patients during the study period, 46 (23.3%) died, 59 (29.7%) were transferred to another unit, 69 (34.8%) were lost to follow up, 24(12.1%) were in active care

A total of 108 patients had CKD stage 5 at final outcome. Seventy-three (67.5%) patients received KRT and a total of 35 (32.4%) were treated conservatively. The different modality of KRT received is shown on Figure 3.3 below.

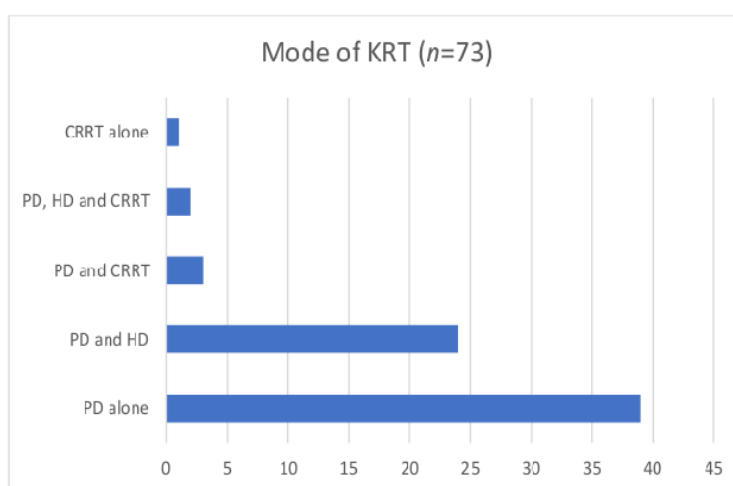


Figure 3. 3 Mode of kidney replacement therapy (KRT) at final outcome (n=73)

3.5. FACTORS ASSOCIATED WITH MORTALITY

The median (IQR) duration of follow up was 1.2 (0.3 to 3.2) years. The mortality rate was 9.8% (7.3-13.1%) person-years (PY), contributed by 46 (23.3%) children. For factors associated with mortality determined by the adjusted Cox regression, patients with CKD stage 5 had 3.5 times (95%CI:1.5-7.9, p-value 0.002) increased risk of death compared to those with CKD stage 3. Patients with albumin <25g/L had 2.6 times (95%CI:1.0-6.2, p-value 0.030) greater risk of death compared to those with albumin $\geq$ 25g/L. Patients with glomerular disease had 2.5 times (95%CI:1.0-6.3, p-value 0.046) risk of death compared to those with CAKUT.

The final adjusted model was assessed for the proportional hazard assumption using the Schoenfeld residuals and the global test gave a p-value=0.1921 which indicates that the proportional hazards assumption was satisfied. Table 3.5 shows variables associated with mortality in patients with CKD stage 3 to 5.

Table 3. 5 Cox Regression Analysis for variables associated with mortality

	<i>n</i> (%)	Univariate Cox regression		Adjusted Cox regression	
		HR (95%CI)	P-value	AdjHR (95%CI)	P-value
Gender					
Female	24(52.1)	1(ref)		-----	-----
Male	22(47.8)	0.6(0.3-1.1)	0.111		
Age group					
2-5 years	11(23.9)	1(ref)		-----	-----
≥5 years	35(76.0)	1.5(0.7-3.1)	0.193		
Residence					
In Gauteng	34 (73.9)	1(ref)		-----	-----
Outside Gauteng	12(26.0)	1.7 (0.9-3.4)	0.096		
CKD stage					
3	9 (19.5)	1(ref)		1 (ref)	
4	6 (13.4)	1.0 (0.3-2.8)	0.977	1.09 (0.3-3.1)	0.863
5	31(67.3)	3.8 (1.8-8.2)	<0.001	3.5 (1.5-7.9)	0.002
Disease					
Glomerular	25 (54.3)	4.1 (1.9-8.7)	<0.001	2.5(1.0-6.3)	0.046
CAKUT	11 (23.9)	1(ref)		1 (ref)	
Other	10 (21.7)	-----		-----	
Haemoglobin					
<11g/dL	38 (82.6)	2.6 (1.2-5.7)	0.012	-----	-----
≥11g/dL	8 (17.3)	1(ref)			
Serum albumin					
<25g/L	20 (43.4)	4.0 (2.1-7.4)	<0.001	2.6 (1.0-6.2)	0.030
≥25g/L	26 (56.5)	1 (ref)		1 (ref)	
Serum bicarbonate					
<22mmol/L	43 (93.4)	3.5 (1.0-11.5)	0.035	-----	-----
≥22mmol/L	3 (6.5)	1 (ref)			
Proteinuria					
<2 plus	14 (30.4)	1 (ref)		-----	-----
≥2 plus	32 (69.5)	2.5 (1.3-4.7)	0.005		

One event time was indeterminate for a female child with CKD stage 5 cause unknown and thus excluded from the Cox regression analysis.

One is equivalent to the reference (ref).

The Kaplan-Meier curve for CKD stages shows that more deaths occurred among patients in Stage 5 (Figure 3.4), and those with glomerular disease (Figure 3.5).

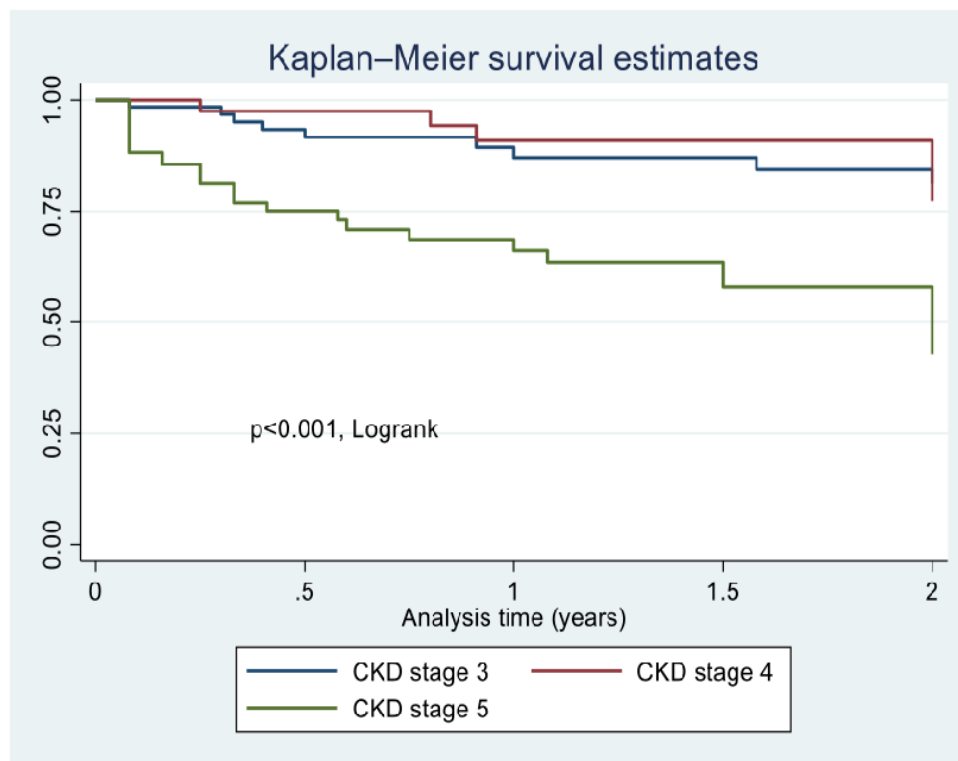


Figure 3.4 Kaplan-Meier survival estimates of CKD stages over a two-year period after diagnosis

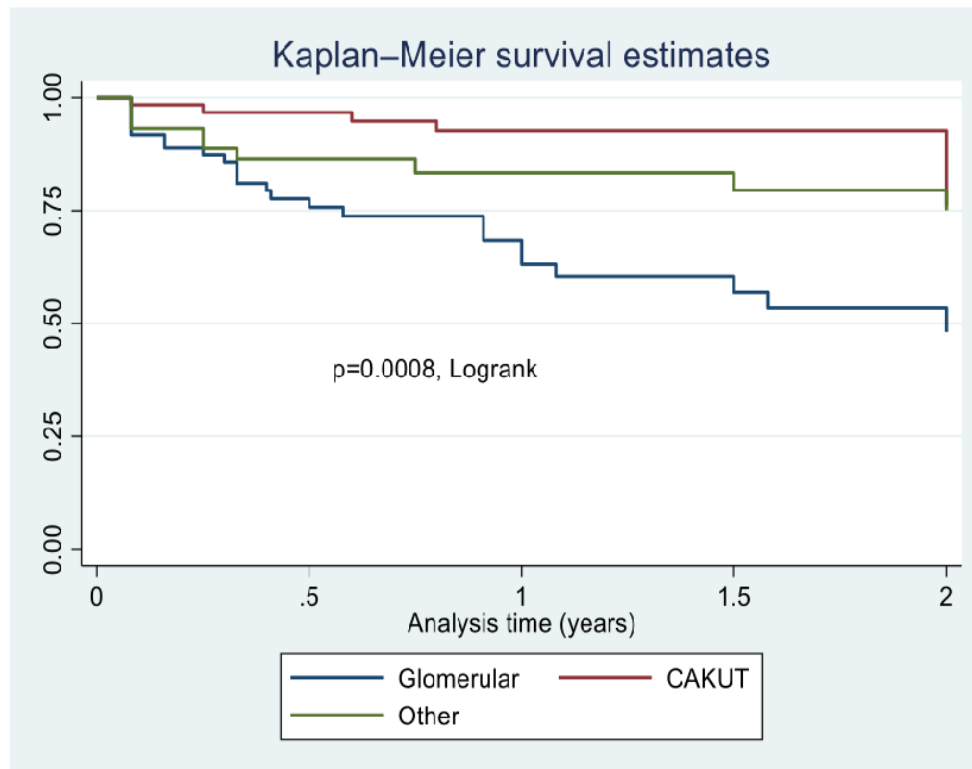


Figure 3. 5 Kaplan-Meier survival estimates of CKD aetiology over a two-year period after diagnosis.

CHAPTER FOUR – DISCUSSION

4.1. DEMOGRAPHICS AND EPIDEMIOLOGY

This study addresses some of the research gaps in South African children with CKD. It provides a calculated incidence rate of CKD stage 3-5 for children in a SA setting, using age-appropriate population indices as supplied by the DHIS. The calculated incidence in our study, for year 2001 to 2019 ranged from 9.3 to 29.7 pmarp. This is higher than other SA studies of CKD in children reporting an incidence of 1–2 per million age-related population in their region (16). The difference could be explained by the different study methods employed.

The calculated incidence rate is similar to the incidence of CKD in children in Europe which is stated to be around 11–12 per million of age-related population (pmarp) for stages 3–5 (50). In the Italkid project, the mean incidence during the period 1995–2000 was 12.1 cases pmarp (range: 8.8–13.9). This however included children with stage 2 CKD (Ccr <75 mL/min/1.73m²) (51).

Incidence rates can be affected by inaccurate values in the numerator or denominator. It may be underestimated by those patients not referred to our centre, missed diagnosis or those seeking alternative medicine. Despite these limitations, this calculated pmarp incidence rate of CKD in children aged two-to-14-year-old in our study should assist Health Economists as South Africa moves to Universal Health Coverage (UHC) and endeavour to attain sustainable developmental goals (SDG) (1).

The median age at diagnosis of CKD stage 3 to 5 in our study was 7 (4–11) years. In the Italkid project, the mean age at registration was 6.9±5.4 years (51). They included patients less than 20 years at the time of presentation and the eGFR using the Schwartz's formula was < 75 mL/min/1.73m² (pre-dialysis). Despite a broader inclusion criterion used in the Italkid project, the ages at registration are similar. In a local study by von Biljon on pre-pubertal children with CKD stages 2 to 4, the mean age at presentation was 4.83 (SD 2.53). Interestingly, in this study, children with non-glomerular disease presented at a younger age compared to those with glomerular disease (52). Similarly, in our study, glomerular disease was the predominant cause of CKD in patients older than 5 years.

In our study, CKD was mostly prevalent in males. This may be due to more congenital abnormalities of the kidney and urinary tract (CAKUT) being prone in males (50).

More than 50% of patients referred from outside Gauteng province in our study had CKD stage 5 at presentation. This reflects late referrals, possibly due to delayed presentation or missed diagnosis. Patients are referred from other provinces such as North West Province (NWP) due to lack of renal services outside of Gauteng Province. Chronic kidney disease is silent before the late stages, which is another factor in delayed presentation.

Patients in our cohort present in advanced stages of CKD with high mortality and morbidity rates, typical of sub-Saharan African countries (2). In a study done in a tertiary hospital in Malawi, 56% of patients presented with CKD stage 3 to 5 (12) and another study in a paediatric renal unit in Cameroon, CKD stage 5 was the most frequent (81.3%) presentation (53). This data identifies a potential area of intervention to improve patient outcomes to meet the SDG.

4.2. AETIOLOGY

4.2.1. NEPHROTIC SYNDROME

In our study, glomerular disease is the most common cause of CKD stages 3 to 5 in children above 5 years of age (43.5%) as well as overall (37.3%), similar to other studies from South Africa and Nigeria (12, 13, 16, 54). This is however contrary to other recent reports from South Africa and Pakistan stating CAKUT as the most common cause in children with CKD (46, 55, 56). This may be due to different study periods and temporal changes in healthcare associated with outcomes. While congenital structural causes such as renal hypoplasia and posterior urethral valves (PUV) are more prevalent in the younger age groups, the incidence of glomerulonephritis does increase in those >12 years of age (50). In a study done in SA, KwaZulu Natal (KZN) on stage 2 to 5 in children, the commonest cause of CKD in all children was nephrotic syndrome, amounting to 36.5% overall (16). This is similar to our study where nephrotic syndrome (37.3%) is followed by CAKUT (32.3%) and genetic syndromes (11.6%) of which primary hyperoxaluria contributed the most (8.0%). Glomerular disease is more prevalent than other renal diseases in Africa and the commonest form of presentation is nephrotic syndrome with age of onset at five to eight years (57). In a single centre study by

Wong et al. in Canada reports glomerular disease accounting for 27% of the overall causes of CKD compared with uropathies, which accounts for 31.1% (58). In Italy, CKD is largely caused by CAKUT (49.1%), steroid-resistant nephrotic syndrome (10.4%), chronic glomerulonephritis (8.1%) (e.g., lupus nephritis, Alport syndrome) and renal ciliopathies (5.3%) (50).

In our study, most children with CKD due to underlying nephrotic syndrome have focal segmental glomerular sclerosis (FSGS) on kidney biopsy. Globally, most children with SRNS have FSGS on kidney biopsy (30). In our study 91.4% of children had SRNS. In a study using the NAPRTCS database, using obstructive uropathy as the referent group, FSGS is the only diagnosis independently associated with a risk of disease progression (HR, 1.77; 95% CI, 1.48 to 2.12) (59).

Two hundred genes are identified to cause the most common aetiologic spectrum of CKD in children, including SRNS; this is not routinely available in SA. Genetic testing has substantial implications such as prenatal testing in affected siblings, genetic counselling and in assessing the patient's prognosis (50). Genetic testing may identify patients in whom immunosuppression for nephrotic syndrome is futile. This is an area of future research which potentially could alter patient outcomes with regard to infections due to immunosuppressive therapy.

4.2.2. HIV ASSOCIATED NEPHROPATHY (HIVAN)

Most patients in our study with HIV related kidney disease were diagnosed between years 2010 and 2019. The number of children with CKD stage 3 to 5 and HIV infection in the four-year period prior to 2004 in our study is 9.0% and 90.9% in the sixteen-year period from 2004 to 2019.

Prior to the implementation of the antiretroviral (ARV) program, the most rapid progressors died in infancy (60). Early diagnosis of HIV and immediate institution of antiretroviral therapy decreased early infant mortality by 76% and HIV progression by 75% (60). The first rollout of the HIV/AIDS program in South Africa in 2004 led to increased testing and survival (61). The estimated proportion of child deaths due to AIDS in South Africa reached a peak of 37–39% around 2005–2006 with a sharp decline towards the end of the decade (62).

There is a wide variety of renal diseases in children with HIV, these include electrolyte and tubular abnormalities, acute kidney injury, thrombotic microangiopathies as well as glomerular diseases that cause proteinuria. The proteinuria can range from asymptomatic

microalbuminuria to complete nephrotic syndrome. Some of the children can progress to CKD (63).

In our study, all patients with CKD due to underlying HIV related kidney disease were diagnosed with a kidney biopsy. A total of 22 (11.1%) of children had HIV related kidney disease in our study of which 21 (10.6%) had HIV associated nephropathy (HIVAN) and 1 (0.5%) had HIV immune complex kidney disease (HIVICK). This is more than reported in the study by Imani et al who demonstrates a prevalence of 1.6% of children with CKD and HIV in their sub-Saharan cohort (64). This may be due to a shorter study period of 6 years in their study or earlier implementation of antiretroviral drugs.

4.2.3. CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT (CAKUT)

In our study, PUV is the most common cause of CAKUT (14.1%) and mostly diagnosed in children 2 to 5 years of age (8.5%). This is similar to a study at a main tertiary paediatric renal centre in Cameroon where of the urological malformations, PUV is the most common cause of CAKUT (53). In a study at a tertiary hospital in Malawi, all patients presenting with obstructive uropathy had eGFR <60ml/min/1.73m² (12). This highlights the late diagnosis or presentations in LMIC countries and the importance of early intervention (12). Considering that CAKUT conditions is the leading cause of CKD in children below age 5 years at diagnosis, foetal anomaly scans, screening ultrasound in children with documented urinary tract infection (UTI), and early referral will allow timeous interventions to prevent CKD (28, 34, 55).

4.2.4. PRIMARY HYPEROXALURIA

In our study, Primary hyperoxaluria is the most common genetic syndrome (8.0%) and presenting mostly above the age of five years. Primary hyperoxaluria type 1 (PH1), a rare autosomal recessive condition, is the most frequent and severe form of primary hyperoxalurias, leading to end-stage kidney disease (ESKD) and systemic organ damage (35, 65). One major hallmark of PH1 in both LMIC and HIC is the delay in diagnosis averaging five years from initial presenting symptoms to diagnosis (65). Chang et al at CHBAH also showed that the median (IQR) age of presentation is 72.0 (44.0-108.0) months and nephrocalcinosis is significantly associated with KF ($p=0.009$) (35). The most common presentation in Chang et al. is urolithiasis, with or without nephrocalcinosis, urinary tract infections (UTIs), haematuria

and KF (35). Screening urine dipstick at primary health care centres or school clinics is a potential public health care tool to identify CKD early.

4.2.5. ACUTE KIDNEY INJURY (AKI)

Although AKI may progress to ESKD, it is seen in a few of the patients with CKD stage 3 to 5 in our study. It is possible that patients diagnosed with mild stages of AKI or who have partial recovery of renal function are not referred to the renal services in our centre. Another reason may be related to the high mortality of AKI in low resource settings (66). Communicable diseases causing septicaemia and diarrhoeal diseases resulting in hypovolemia and septic shock, herbal medication from alternative medicine and malaria are common in LMIC and have a role in causing AKI (53). Most patients in a study in a tertiary hospital in Malawi with AKI show improvement in their glomerular filtration rate and a minority progress into CKD stage 3 (12). In an adult review article by Coca et al. reports that AKI increases the risk of CKD by 8-fold (HR ¼ 8.8, 95% CI 3.1–25.5) and the risk of end-stage kidney disease by 3-fold (HR ¼ 3.1, 95% CI 1.9–5.0) (67). In an adults and paediatric review study of AKI in sub-Saharan Africa, 11 studies report dialysis needed acutely in 1042 of 1572 (66%) children with AKI; Five (0.8%) children with AKI in that study during 1998 to 2020, developed chronic kidney disease (66). Raising awareness of the risk of AKI progression to CKD and appropriate screening for CKD in this population is possible area of intervention to improve outcomes.

4.3. RISK FACTORS

In our study risk factors were identified in 35 (17.6%) patients. The retrospective nature of the study could be under-representing risk factors. Most of the risk factors could be identified in the neonatal period. This represents an opportunity for intervention and screening starting in the neonatal period.

In general, risk factors for CKD include small for gestational age, low birthweight and prematurity and are more common in LMIC. These perinatal conditions increase the risk of proteinuria, hypertension, and CKD in later life (28, 68, 69, 70, 71, 72) through multiple methods including low nephron numbers (68, 69, 70, 71, 72).

Interestingly in the CKiD cohort, the rate of change in GFR over time did not differ significantly between children with abnormal birth history (defined as SGA, birthweight < 2500 g, or gestational age < 36 weeks) and those without thus suggesting that other factors may be at play. (73). This could also be explained by the short follow up period of 4 years.

Strategies could be implemented in neonatal outpatient clinics to screen patients with risk factors for chronic kidney disease and early referral to nephrology services.

4.4. COMPLICATIONS

In our cohort, complications of CKD at initial diagnosis significantly progressed with advancing stage of CKD

4.4.1. ANAEMIA

Anaemia in children with CKD is a serious leading to decreased ability of daily activities such as exercise and cognitive abilities, thus leading to poor quality of life (50). It also causes progression of cardiovascular risk factors such as left ventricular hypertrophy (LVH) (50). As in adults, the goal of treatment is to achieve target haemoglobin levels of approximately 11 g/dL or slightly greater. (50).

In our study, anaemia ($p=0.0001$) is more prevalent in children with CKD stage 5 [8g/dL (6.3 to 9.7)] compared to CKD stage 3 [11g/dL (9.3 to 12.6)] and stage 4 [10.4g/dL (8.95 to 11.32)].

This underscores the need for screening, as early diagnosis of CKD provides an opportunity to treat the anaemia and its complications.

In a single centre study by Wong et al., anaemia (using the KDOQI cut-off of a haemoglobin <12 g/dL) is present in 36.6% of the overall cohort. The prevalence of anaemia increased from 31% at stage 1 to 93.3% ($P<0.001$) at stages 4 and 5 (58). Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) shows that the prevalence of anaemia in children is 73% at CKD stage III, 87% at stage IV and >93% at stage V (50). In another local study by Mudi et al, there is a high prevalence (41/130; 32%) of anaemia among the patients with CKD stage one to five (39).

In our study the serum ferritin is significantly greater in the patients with CKD stage 5, likely signifying an inflammatory response or due to blood transfusions. It is not uncommon for

patients with CKD to have normal or elevated ferritin levels as a sign of inflammation and not necessarily total iron body stores (50). Supplemental iron therapy (either oral or intravenous) is necessary for the treatment of anaemia in children with CKD. Data on iron supplementation was not collected in our study. In a local study by Mudi et al., serum ferritin and RCDW were the only independent predictors for anaemia, iron deficiency and iron deficiency with anaemia ($p < 0.050$) (39). There are other important causes of anaemia including erythropoietin (EPO) deficiency (39). This was not assessed in our study.

Despite use of EPO, iron supplementation and blood transfusions, anaemia is difficult to correct even in HIC (50). Hepcidin has an important role in contributing to anaemia in patients with CKD. It is a peptide produced in the liver and is inappropriately high in patients with CKD and thus leading to increased iron storage (high ferritin) and decreased free iron for erythropoiesis (low serum transferrin saturation (TSAT)). The hypoxia-inducible factor (HIF) pathway is also essential in inducing erythropoiesis (74). This has been an area of research and newer agents have become available (74).

Anaemia is a risk factor for mortality, discussed in the next section 4.6.

4.4.2. METABOLIC ACIDOSIS

Epidemiologic studies demonstrate that lower serum bicarbonate is associated with an increased risk of kidney disease progression (75). In our study, the median serum bicarbonate value decreased significantly with advancing stages of CKD. This reflects progression of metabolic acidosis in more severe forms of CKD stages.

In our study, a serum bicarbonate < 22 mmol/L is a significant risk factor for mortality in the univariate analysis ($p = 0.035$) but not in the multivariate analysis. In a single center adult retrospective cohort study involving patients with kidney disease of which 9% with a baseline eGFR < 60 ml/min/1.73m², the risk of CKD progression i.e., decline in the eGFR by 50% or reaching an eGFR of < 15 ml/min/1.73m², in the multivariate analysis was 1.54 (95% CI: 1.13-2.09) with bicarbonate levels < 22 mEq/L compared with bicarbonate levels of 25 to 26 mEq/L (76).

Metabolic acidosis is also observed in earlier stages of CKD, especially in renal disease with tubular dysfunction such as CAKUT or chronic tubulointerstitial nephritis (77). This represents an area of research and optimization of acid-base in children with CKD to slow down progression.

4.4.3. MINERAL AND BONE DISORDER

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is represented by abnormalities in calcium, phosphate, parathyroid hormone (PTH) and Vitamin D metabolism. This affects children's linear growth and can cause vascular or soft tissue calcifications (50). Renal osteodystrophy, another feature of CKD-MBD, is diagnosed by histology (50).

In our study none of the patients have vascular or soft tissue calcifications documented. Our study shows significant progression of calcium ($p=0.0001$), phosphate ($p=0.0001$) and parathyroid hormone ($p=0.0008$) with increasing CKD stage, with severity increasing in patients with CKD stage 5. This highlights disease severity with progressing stage of CKD. In single centre study by Wong et al the prevalence of metabolic bone disease was as high as 15.09% in stage 2 disease, 47.37% in stage 3, and 100% in stages 4 and 5 CKD (58). In a study using the NAPRTCS database, patients with hypocalcaemia at time of registration had a 29% higher risk for renal progression independent of other factors (HR, 1.29; 95% CI, 1.06 to 1.58) compared to patients with normal serum calcium. In addition, hyperphosphatemia posed a 41% increased risk of renal progression compared to normal serum phosphate, (HR, 1.41; 95% CI, 1.25 to 1.59) (59). Prospective studies at our site may provide more accurate prevalence of CKD-MBD.

The reason for emphasis on prompt management of CKD-MBD is to slow down stunting as well as bone remodelling. More importantly, phosphate is a potent vascular toxin by itself or by its effect on PTH and fibroblast growth factor 23 thus leading to progression of cardiovascular disease as emphasized below (50).

4.4.4. CARDIOVASCULAR DISEASE

One of the most important aims of treating complications of CKD is to reduce the cardiovascular risk of death. As in adults, cardiovascular disease (CVD) is the leading cause of death in the paediatric CKD population, with a risk 1000 times higher in the ESKD group compared with paediatric group without CKD. (50).

In our study, at diagnosis, 111 (56.0%) patients had hypertension. Hypertensive heart disease was documented in 63 (31.8%) on echocardiogram.

Risk factors for cardiovascular disease in children with CKD include steroid therapy, as well as risk factors specific for CKD such as hyperphosphatemia, hyperparathyroidism and anaemia

(50). This can lead children to die from arrhythmias, valve disease, cardiomyopathy as well as cardiac arrest (50).

4.5. KIDNEY FAILURE TREATMENT OUTCOME

In our study, seventy-three (67.5%) patients received KRT. Most of the patients in our study received peritoneal dialysis. Peritoneal dialysis is still the first choice of dialysis in our cohort as is also represented in most countries with limited resource, including South Africa (17, 78)

It is estimated that annually at least 1,000 children might require KRT in South Africa (79). However less than 10% is estimated to be able to get access to KRT in South Africa (79).

Although in South Africa access to KRT is state-funded and is supposed to be accessible to all children, the reality is that the financial burden placed on the family of a child with ESKD becomes insurmountable (79). This is compounded for patients travelling from Provinces where Paediatric Nephrology Services are not available. Even for those children who have access to private health insurance, the non-medical cost burden on the family can still be significant leading to a need for social and financial assistance (79). A total of 35 (32.4%) of patients in our study were treated conservatively. The underlying factors leading to CKM was not explored in this study. The Pediatric Feasibility Assessment for Transplantation (pFAT) tool developed at Red Cross Children's Memorial Hospital allows standardization of eligibility of children with CKD for transplantation in a resource limited setting (46). For various reasons including parents' choice, poor social circumstances, distance from centre, severe illness and non-South African nationality. This is decided upon after careful discussions in a multi-disciplinary team with the family. Conservative kidney management is regarded globally as one of the active treatment modalities for patients in kidney failure in addition to dialysis and kidney transplant. It is not regarded as "doing nothing", instead it aims at slowing the progression of kidney disease and managing the complications of disease (45).

The mortality rate in our study was 23.3% and there is a high lost to follow up percentage of 34.8%. This may be due to patients seeking alternative medicine, distance from renal centres or early death from complications of CKD. In the study in Cameroon by Halle et al reports a mortality rate of 50%, their mortality rate could be explained by severity and type of renal disease at presentation and lack of chronic dialysis infrastructures and affordability (53). This

is similar to a systematic review in sub-Saharan Africa done by Ashuntantang et al., in both adults and paediatrics patients with ESKD shows a mortality rate of 62% in the paediatric population (80). Compared to other African countries, dialysis in South Africa is state funded thus allowing the children to have better access to KRT and thus contributing to our lower mortality rate. However, it should be noted that the mortality rate in our cohort may be underestimated because the outcome of patients transferred to the transplant centre is not known.

4.6. RISK FACTORS FOR MORTALITY

In our study, glomerular disease, hypoalbuminemia, and CKD stage 5 at presentation is a significant risk factor for mortality in the multivariate analysis, increasing the risk of mortality by 2.5, 2.6 and 3.5-fold respectively. This is similar to other studies (37, 56, 81, 82). Kamath et al. on multivariate analysis, identified glomerular disease amongst other variables to be a risk factor for progression of CKD (82). On the Kaplan-Meier survival curves in our study, patients with glomerular disease had greater mortality over time compared to those with CAKUT. This supports the notion of slower advancement to ESKD in patients with CAKUT, compared to those with glomerular diseases (50).

The mean rate of decline in eGFR from baseline to final visit in our study was similar to another study from the Latin American Registry which reporting a rate of 5.8 ml/min/BSA per year (82). In a local study by van Biljon, the rate of decline in GFR in pre-pubertal children with glomerular vs non-glomerular disease, was more than 5 mL/min/1.73 m²/year in 82% of patients with glomerular compared with 5% with non-glomerular disorders (52). Our mean rate of decline in eGFR is however higher [4.90 (SD 7.03) ml/min/BSA per year] compared to the study by Kamath et al (82). This may be due to inclusion of CKD stage 2 in their study as well as a short follow up period (82).

Anaemia and proteinuria are documented risk factors for mortality in children with CKD (59, 83). In our cohort, although identified as risk factors on univariate analysis, significance is not demonstrated on multivariate analysis.

4.7. STUDY STRENGTHS AND LIMITATIONS

The study is limited by its retrospective nature and missing information on outcomes for patients who have not returned for scheduled appointments. Referral bias may overrepresent certain diagnoses, and patients not referred or who died at the peripheral hospitals may underestimate the incidence rates. Despite these limitations, the strengths of this study spanning over two decades is able to demonstrate the spectrum of CKD in children. This is the first study in SA to calculate the annual incidence rate of CKD stage 3 to 5 in children. The study describes the risk factors associated with mortality and makes clear recommendations for interventions and areas of research in prospective studies.

CHAPTER FIVE – CONCLUSION

The spectrum of chronic kidney disease is predominantly glomerular in our population, similar to other countries in Africa and Sub-Saharan Africa (12-13, 16, 18, 54, 57). This study highlights the need for screening programs for the general paediatric population, in particular those of pre-school going age for glomerular diseases and re-enforcing antenatal screening for CAKUT and early management of both diseases.

The calculated incidence in our study is higher than previously stated in other South African studies (16). The high incidence is concerning because it is only a reflection of the proportion of referrals to our facility and excludes those that are not referred. The calculated incidence reflects the burden of CKD not previously documented in South Africa and Africa (79).

Even though South Africa is labelled an UMIC, the reality is there is still a huge gap between the majority of South Africans who rely on limited resourced public health care system and those that can afford private health (17, 79). This is further compounded by the limited number of trained paediatric nephrologist in South Africa, most of which are found in tertiary health care centers thus leaving the peripheral hospitals in other provinces without paediatric renal expertise. The lack of Paediatric Renal services in other Provinces contribute to late referrals (84). In addition, the social determinants of health, health-seeking behaviour, cultural and religious beliefs all impact on delayed diagnosis and compliance of follow-up (16). Unfortunately, these factors also impact on the feasibility for kidney transplantation (46), which may partially explain the rate of conservative therapy in this population. Low- and middle-income countries are challenged not only by lack of renal centres, but also by the limited resources such as dialysis (58, 79).

Our study demonstrated that the mortality in patients within our region is significantly associated with glomerular disease, hypoalbuminemia and children presenting late in end stage kidney disease. The Department of Health in South Africa emphasises the importance of acting decisively to prevent and combat non-communicable diseases (NCDs), including kidney diseases (85, 86). This is important as South Africa moves into Universal Health Coverage as well as fulfilling the SDG in 2030. It is proposed that all concerned, including government and

nonstate actors, must put more effort into prevention and guidelines on screening and treatment of kidney disease (86). The results of this study may provide guidance in this regard.

5.1. RECOMMENDATIONS

This study proposes the following recommendations to identify kidney disease early with appropriate referral to nephrology specialist services:

- 1) Implement targeted screening programs at the primary health care level using urine dipstick and blood pressure readings to identify glomerular disease or CKD early in order to implement early preventative treatment.
- 2) Neonates with known risk factors such as prematurity, neonatal AKI, birth asphyxia, family history of kidney disease, abnormal foetal anomaly scan could be screened at neonatal follow-up clinics- screen for chronic kidney disease.
- 3) Inpatients diagnosed with AKI- screen for chronic kidney disease and document time to progression to CKD.
- 4) Training of Paediatric Nephrologists in Provinces where these services are not available which may decrease late referrals and disease severity upon presentation.

5.2. FUTURE RESEARCH

Future research such as prospective studies on the influence of hypertension in children with CKD in our regions is important and was not investigated in our study. It is also important to look at the cause of death and kidney transplantation rates in children with moderate to severe CKD. A national Paediatric CKD registry including the patients managed conservatively will provide valuable data on the current situation. These studies should focus on the development of protocols to help alleviate the burden of this disease in South Africa. Studies exploring the psychosocial burden on families are underway in the unit. Other areas of potential research include obtaining funding for genetic testing for various kidney conditions; prospective follow up studies on early screening of risk factors in the neonatal period and its association with eGFR decline rates, and research on early optimization of hypoalbuminemia in CKD and outcomes on patient mortality.

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