Clinical profile and outcome of autosomal dominant polycystic kidney disease at a tertiary hospital KwaZulu-Natal, South Africa
A retrospective 5-year review

By

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Submitted in partial fulfillment of the academic requirements for the degree of MMed
Department of internal medicine
School of Clinical Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban/2022

As the candidate's supervisors I have approved this thesis for submission

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Declaration

I, Taha Mohamed Abulghasm declare that:

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Dedication

This thesis is dedicated to the memory of my late parents, Mohamed Abulghasm and Khadija Eltheni. They instilled in me a desire to learn and the value of hard work and good education with their ongoing prayers, love, and support.

To my lovely wife: Amna Belhassan Ahmed. You have been the most significant source of support and encouragement throughout this educational journey.

To my wonderful children: Kais, Albaraa, and Miral. You are my pride and joy.

To my brothers, sisters, and extended family: Your encouraging words gave me the strength to make this dream a reality.

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Overview of the Thesis

Background of the study

Autosomal dominant polycystic kidney disease (ADPKD) is the commonest inherited kidney disease with two identified genetic defects, PKD1 and PKD2. It affects both genders equally; however, male patients may have more severe phenotype. Furthermore, kidney function declines over many decades. Up to 10% develops end stage renal disease (ESRD). Alcohol, caffeine consumption and hormonal estrogen therapy are risk factors for cystic kidneys disease. Polycystic liver and cerebral aneurysm are the most common and serious extra-renal manifestations of ADPKD. Although hypertension is common finding, most patients remain asymptomatic in the early stages. Sub-nephrotic proteinuria is often seen in ADPKD patients. ADPKD is commonly diagnosed by age-dependent unified ultrasonographic findings (Ravine's criteria).

Randomized trials that compared novel therapies of ADPKD and the Food and Drug Administration (FDA) have approved the use of tolvaptan as a novel medication in those ADPKD patients whose kidney function decline is rapidly worsening. Reno-protection strategies such as blood pressure control, risk factor reduction and avoidance of nephrotoxins remain the mainstay of treatment. Literature is scarce regarding ADPKD in the region of sub-Saharan Africa. This study aimed to investigate the demographic, clinical profiles, and outcomes of patients with ADPKD at a specialized tertiary center in Durban, KwaZulu Natal, South Africa.

Methods: A retrospective review of 81 ADPKD subjects was conducted at Inkosi Albert Luthuli Central Hospital (IALCH) from January 2013 to December 2017. Ravine's criteria established the diagnosis based on ultrasonography and CT scan and MRI reporting findings. This chapter analyzes the demographic and clinical parameters and Laboratory results as well as treatment outcomes, which were captured from medical records. Renal replacement therapy, transplantation, and nephrectomy were the outcome.

Ethical approval was granted by the University of KwaZulu-Natal's Human Research Ethics Committee (ref. no. BE081/19)

Statistical analysis: Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27. Categorical variables were described as numbers and percentages and compared using the Chi-square test, Fisher's exact test, or Fisher-Freeman-Halton exact test, where appropriate. Continuous variables were analyzed using the Kolmogorov-Smirnov test for normality. As many continuous variables had a non-Gaussian distribution, all continuous variables were described using the median and interquartile range (IQR) and compared using the Mann-Whitney U-test or related-samples Wilcoxon Signed Rank test, as appropriate. A p-value of <0.05 was deemed statistically significant.

Results: Forty-four percent were Indians; Females were predominance with a median age of 55 years. Hypertension was present at 95.1%, and abdominal pain was the main presenting complaint (28.4%). Hematuria was prevalent in 22.9%, and only 4 patients had UTI with no gender predilection. Approximately 57.0% of patients were not anemic with a hemoglobin greater than 11 g/dL. A liver cyst was the predominant extra-renal manifestation. Significant proteinuria and raised CRP were seen in ESRD patients on kidney replacement therapy, which was the predominant outcome (42.0%). Nephrectomy and kidney transplantation were rare (6.2%).

Conclusion: The clinical profiles and outcomes were comparable to other literature elsewhere. Females were predominant. Further studies are required to determine the best novel medical treatment in Sub-Saharan Africa with the impact of HIV infection. Screening testing of ADPKD relatives is highly recommended.

Table of Contents

Abbreviations

- ADPKD: Autosomal Dominant Polycystic Kidney Disease
- ACEIs: Angiotensin converting enzyme inhibitors
- ARBs: Angiotensin receptor blockers
- ART: Anti-Retroviral Therapy
- BP: Blood Pressure
- CRP: C- Reactive protein
- CRRT: continuous renal replacement therapy
- CKD: Chronic Kidney Disease
- CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
- CT scan: Computer Tomography scan
- cAMP: cyclic Adenosine Monophosphate
- CVA: Cerebro-vascular accident
- CVS: Cardio-vascular system
- ESRD: End stage renal disease
- eGFR: estimated Glomerular Filtration Rate
- FDG-PET: Fludeoxyglucose positron emission tomography
- GIT: Gastrointestinal tract
- HIV-Human Immunodeficiency Virus.
- ht-TKV: age and height-adjusted Total kidney volume
- iGFR: iothalamate clearance Glomerular Filtration Rate
- IALCH: Inkosi Albert Luthuli Central Hospital.
- IQR: Interquartile Range
- ICA: Intra cerebral aneurysm
- KRT: Kidney replacement therapy
- KZN: KwaZulu-Natal
- LVH: left ventricular hypertrophy
- MCS: Microscopic culture and sensitivity
- MCKD: Medullary cystic kidney disease
- MLPA : Multiplex-dependent probe amplification
- MRA: Magnetic resonance angiography
- MRI: Magnetic Resonance Imaging

- MSK: Medullary sponge kidney
- mTOR: Mechanistic target of rapamycin
- NSAIDs: Nonsteroidal anti-inflammatory drugs
- PC-1: Polycystin 1
- PC-2: Polycystin 2
- PKD1: Polycystic Kidney Disease1
- PKD2: Polycystic Kidney Disease2
- RAAS: Renin-Angiotensin-Aldosterone System
- RCC: Renal cell carcinoma
- RNA: Ribonucleic acid
- RRT: Renal replacement therapy
- SA: South Africa.
- SAHS: South African Hypertension Society
- SPSS: Statistical Package for the Social Sciences
- TKV: total kidney volume
- UPCR: Urine protein creatinine ratio
- UMCS: urine for microscopy and culture sensitivity
- UTI: Urinary tract infection
- VHL : Von Hippel–Lindau

Tables and Figures

Table 1: Baseline demographic data and comorbidities

Table 2: Clinical and outcome data

Table 3: Imaging data

Table 4: Urinalysis data

Table 5: Biochemical data

Table 6: Variables with significant associations with ESRD (excluding urea, creatinine and GFR)

Part 1: The Review of Literature

Chapter One

Introduction

Polycystic kidney disease can be either familial (genetic) or acquired. Autosomal dominant type (ADPKD) is the commonest inherited kidney disease run through the family; that classically appears in two forms (ADPKD1) and (ADPKD2). In contrast, the other infantile pattern affects children predominantly and is called autosomal recessive polycystic kidney disease (ARPKD).

ADPKD is a genetic mutation with two defective PKD1 or PKD2 genes. It is characterized by delayed onset symptoms based on the size of kidney cysts that grows and impact kidney function leading to hypertension and ends with stage-5 kidney failure (ESRD), however, both ADPKD forms can remain asymptomatic for several decades before renal dysfunction is evident [1]. Many recent studies have been conducted on the novel therapies of the disease. In this study, we outline the review of different clinical profiles, laboratory tests, and radiological images of ADPKD in the South African context.

Epidemiology

ADPKD was first described in the 1900s in a Portuguese medical journal by Dr. Custodio Cabeca. The incidence of 1 in 800 was estimated based on autopsy results with no racial or gender predilection. However, ESRD in ADPKD populations in the United States is more in men [2]. Although ESRD develops late in ADPKD, it remains the 4th leading cause of kidney failure globally (> 5%). Nowadays, due to easy access to kidney replacement therapy and the minimal number of cardiovascular deaths in ADPKD, the onset of ESRD is found to be later.

Pathophysiology

The molecular mechanisms and function of polycystins in ADPKD pathogenesis are still poorly understood. The PKD1 and PKD2 genes are found to be expressed in different organ tissues such as primary cilia of the nephrons, biliary ducts, peribiliary glands, pancreatic ductal epithelium, and other various tissues in the body. These gene products interact with the regulation of intracellular calcium, flow-mediated mechanosensation as well as cell-cell interactions like tight junctions that will lead to abnormal epithelial cell proliferation [3]. It is reported that only a small percentage of tubules develop cysts, and the initiation of cystogenesis requires somatic mutations to the normal allele PC-1 or PC-2. The epithelial cells proliferate in response to a variety of signals; vasopressin signaling may be impaired so that these affected cells respond abnormally to the increased rate of cyclic adenosine monophosphate (cAMP). Also, damping the signaling pathways that are responsible for tubulogenesis impairment give a chance for more generation and cystic formation. The disease severity is estimated by the progression rate of cyst growth as well as PC-1 [4]. As the cysts enlarge, they become walled off

from the rest of the collecting system, explaining the cystic hemorrhage and infection, which may not be evident in the urine. Resistant hypertension and interstitial fibrosis were reported in some cases as a consequence of enlarged cyst due to blood flow impairment to normal nephrons.

In brief, kidney cysts are growing gradually in numbers and size, and the nephron's epithelia of the distal and collecting duct induce the inflammatory response by releasing cytokines.

Genetics

ADPKD has a Mendelian autosomal dominant inheritance pattern, which means the affected patients carry a 50% chance of inheriting the mutated gene from their children. There are two well-defined causative heterogeneous genes, the commonest one called PKD1 gene present on chromosome 16 and encrypt polycystin 1 (PC-1). In contrast, the other PKD2 locus on chromosome 4 is less common and it encrypts polycystin 2 (PC-2). However, in Canada and United States the prevalence of PKD2 was higher than that documented elsewhere. The genotype-phenotype relationship is not clearly understood because the disease has a variety of phenotypes from newborn to adulthood, which is determined by the identity of an affected locus (PKD1 vs. PKD2 mutation), the timing of gene inactivation, and genetic background [5]. In the same family, the disease severity may vary, suggesting the role of genetic and environmental influencing factors. De novo mutations were reported in a few cases with a negative family history of ADPKD.

Diagnosis: Is often delayed because most cases are asymptomatic until late in the disease course. It is frequently discovered incidentally on abdominal imaging performed for an alternate indication. ADPKD-specific reasons for ultrasonography include unexplained deranged renal function, early-onset hypertension, or abdominal pain from either cyst expansion, hemorrhage, or infection.

- History: focused on positive family history of RRT such as dialysis or renal transplant and the age onset of ESRD. Also, presence of cerebral aneurysms or sudden unexplained deaths in the family must be ascertained, as this would put patients at risk for similar events and necessitate further screening measures. A personal history of recurrent headaches or neurological symptoms must be sought. Flank and abdominal pain may be suggestive of symptomatic renal or hepatic cysts. A history of hematuria, dysuria, and nephrolithiasis should be investigated. Caffeine intake should be quantified. In women, the history of estrogen exposure (pregnancy, contraception, hormone replacement therapy) should be assessed.
- Physical Examination: This is often normal in the early stages of ADPKD. The first sign of ADPKD is frequently young hypertension. As the kidneys progressively enlarge, the cysts may be palpable on abdominal examination. Hepatic cysts may also be palpable and elicit epigastric tenderness. Cardiac auscultation may reveal the mid-systolic click of mitral valve prolapse.

Clinical presentation (Renal vs Extra-renal):

Although the age of onset of symptoms is variable even among the family members, haematuria, hypertension, abdominal pain and distention, proteinuria (with or without) a decline in glomerular filtration rate are still the main classical presenting signs and symptoms. The two primary forms of ADPKD overlap with quite similar clinical presentations.

Renal Manifestations and Complications:

- **Hematuria:** Commonly seen in ADPKD patients and resolve within a couple of days after the onset. Frank hematuria indicates nephrolithiasis, bleeding, or infection within the cysts. Renal neoplasm is far less common, but it is still to be considered and investigated if the patient is older than 50 years and has persistent hematuria. Management is mainly conservative by optimizing euvolemic status, bed rest, and avoid all precipitants such as anticoagulants, and antiplatelet agents [6]. Blood transfusion in severely anemic or those with active bleeding is advised with caution to use leucodepleted ones to prevent sensitization in potential future kidney recipients. In refractory cases, tranexamic acid is also recommended.
- **Abdominal and flank pain:** Acute pain has been reported in two-thirds of ADPKD patients with variable characteristics based on the underlying causes, colicky radiating pain in renal stones, unilateral and non-radiating pain as seen in infected cysts as compared to the point tenderness in hemorrhagic cyst. It can be insidious (chronic), which is usually due to an enlarged cyst as well as an expanded and stretching capsules in the kidneys or the liver. It is typically a dull aching in nature, aggravated by standing and mobilization. The management includes physiotherapy, painkillers like nonsteroidal anti-inflammatory drugs (NSAIDs), and Opioids which are to be given with caution and adjusted for GFR in elderly patients [7]. Cyst sclerotherapy, percutaneous cyst aspiration, nerve blockade (celiac plexus blockade), laparoscopic kidney denervation, and sympathosplanchnicectomy are alternative treatment modalities to be attempted in those with incapacitated pain.
- **Cyst hemorrhage:** self-limited disorder, may persist for up to 2 weeks and can be very painful and associated with fever. Because the cysts may become walled off from the rest of the urinary tract, hematuria is not always present. However, subcapsular, or retroperitoneal hematomas are rarely seen. Hemorrhagic cyst is treated conservatively with oral hydration, bed rest, and analgesia.
- **Cyst infection:** typically presented as an upper UTI with classic symptoms of fever, loin pain, dysuria, and pyuria. However, the presence of bleeding within the cyst causes minimal lower urinary tract manifestations with a negative urine culture. Urinalysis and septic screening is

considered to be part of the initial testing. It is noted that the FDG-PET scan is more sensitive than the other radio-imaging studies in detecting cyst infection [8]. Treatment with parenteral antibiotics with good cyst penetration properties like ciprofloxacin, sulfamethoxazole-trimethoprim, or chloramphenicol for at least 6 weeks has shown good outcomes. However, resistance to antibiotics has been reported in those with recurrent pyrexial episodes, an enlarged cyst of more than 45mm, and/or a complicated infected cyst. The best treatment option to take place is surgical drainage.

Of note! In those with a complicated perinephric collection (abscess) or emphysematous pyelonephritis, nephrectomy is to be considered.

- **Nephrolithiasis:** uric acid and calcium-based stones are frequently reported in ADPKD patients. Therefore, a full metabolic workup is to be performed in ADPKD patients with nephrolithiasis to investigate for hypocitraturia, hypercalciuria, and hyperuricosuria [9].
- **Hypertension:** most common presenting sign with early onset at the age of 30 years, it accounts for more than two-thirds of patients with ADPKD. Local ischemia from stretching and compression of expanded cysts activates the renin-angiotensin–aldosterone axis that elevates blood pressure. Recently noted that ADPKD patients have less cardiovascular impaction, which is attributable to the optimal control of BP, that's why frequent BP monitoring even in the young adult population is highly recommended. Management is always based on lifestyle modification through regular exercise, diet control with low salt, and optimal medical treatment using aldosterone antagonists (ACEIs or ARBs) as first-line agents. Calcium channel blockers and diuretics are also recommended as a second line. A concentrating defect is generally mild and may be seen early in the disease course; this may be accounted for by vasopressin receptor (V2) signaling abnormalities [10].
- **Proteinuria:** moderate subnephrotic proteinuria of (0.15 g/d – 0.5 g/d) was reported in 25% of ADPKD adults but rarely reached more than (1.0 g/d). It is considered as a value for prognostication purposes as it correlates directly with disease severity (i.e., rapid decline in renal function with early ESRD reported in those with larger total kidney volume (TKV). If the nephrotic range of proteinuria is present, the superimposed glomerular involvement is to be considered [11]. It is still undetermined whether using ordinary anti-proteinuric agents like ACEIs or ARBs will be beneficial in slowing the disease.
- **Renal Cell Carcinoma (RCC):** Rarely seen in ADPKD, only < 1% of cases. It is multicentric sarcomatous in type that usually involves both kidneys. RCC can be detected on ultrasonography that shows cystic or solid mass. Speckled calcifications and enlarged regional

lymphadenopathies can also be seen on contrast-enhanced CT or MRI. No routine screening test is recommended for RCC.

Extrarenal Manifestations: ADPKD patients have numerous extrarenal manifestations that pertain to mortality and morbidity, such as:

- **Liver cysts:** Commonest extrarenal manifestation with a prevalence more than 75%. The majority of polycystic liver disease patients are asymptomatic. However, some of them might present with organic or functional dyspepsia in form of reflux symptoms, flatulence, and abdominal discomfort. While very few patients, especially multiparous women, and those on long-term oestrogen, have reported hepatic decompensation as a consequence of venous-occlusive disease. The treatment is mainly conservative in order to improve the quality of life; however, some polycystic livers can get infected, ruptured, or bleed, that requires further intervention either by drainage, sclerotherapy, surgical unroofing, or partial liver resection in those who are not a good candidate for liver resection [12]. Liver transplantation is the last resort. Using Somatostatin analogs either octreotide or lanreotide, have shown significant reduction and marked shrinking of the liver cysts; however, they are still not yet approved for slowing disease progression. An infected hepatic cyst has been reported in polycystic liver disease. Using standard imaging MRI and CT scans has non-specific findings and because FDG-PET is more sensitive, it's highly recommended for making a definitive diagnosis. The treatment entails parenteral or oral broad-spectrum antibiotics with good cyst penetration capability (e.g., quinolones).
- **Cerebral aneurysms:** This is the most serious extrarenal manifestation with a higher incidence rate in those with a strong family history of cerebral aneurysms or history of sudden unexplained death compared to the general population (2%). Rupture aneurysm is the leading cause of death in more than half ADPKD-ICA population. Thunderclap headache is the early manifestation, and it's pretty common in those who have poorly controlled hypertension or a history of subarachnoid hemorrhage. Symptomatic patients with or without a family history of ICA should undergo magnetic resonance angiography (MRA). The screening test is only indicated in some instances, such as those requiring initiation of anticoagulation, high-risk occupational group (e.g., pilots), and/or patient who needs surgery. ADPKD patients with small aneurysms (<7 mm) need serial follow-up, while the high-risk group patients should undergo repair. Inconclusive imaging in risky patients also needs interval scans for 10 years [13]. The cornerstone of management is based on risk factors modification by blood pressure control, quitting smoking and alcohol intake. A multi-professional collaborate of neurosurgeons,

neurologists, and interventional radiologists are needed. Endovascular embolization is preferable to surgery. Serial imaging is mandatory to post procedure starting at 6-month intervals, annually, and then every three years if stable patient.

- **Valvular heart disease:** mitral valve prolapse is not uncommonly seen in ADPKD patients. However, dilated cardiomyopathy and small pericardial effusion are rare. Aneurysms of large arteries have been reported [14].
- **Abdominal Hernias:** are more frequent in ADPKD under peritoneal dialysis.
- **Solid organ Cysts:** Rarely seen, but pancreatic, seminal vesicle cysts, as well as meningeal cysts of the spine, have been reported in ADPKD patients.
- **Colonic diverticulitis:** carries a high risk of bowel perforation and is seen very often in ADPKD.

Management

Diagnostic Criteria: Age-dependent ultrasound criteria have been established for patients at risk of developing ADPKD. A combination of positive family history, number of kidney cysts on imaging, and the constellation of extra-renal manifestations (e.g., liver cysts) is enough to diagnose ADPKD. Although genetic testing is needed in some cases, imaging studies remain the pillar. Ultrasonography is the imaging of choice for pre-symptomatic diagnosis because of non-invasive, cheap bedside test, and easy to access; however, it requires skilled hands. The classical findings are enlarged kidneys with multicystic lesions. If the ultrasound findings are inconclusive or equivocal, an MRI abdomen is necessary to establish a diagnosis.

- Ultrasonographic diagnostic (Ravine's) criteria for PKD [15]:

⇒ <30 years: ≥ 2 cysts, either unilateral or in both kidneys, with positive family history.
(Or presence of≥ 5 cystic lesions bilaterally in the absence of family history).

⇒ 30-59 years: ≥ 2 cystic lesions in each kidney with positive family history.
(Or presence of≥ 5 cystic lesions bilaterally in the absence of family history].

⇒ ≥60 years: at least four cyst in each kidney regardless of family history

For that above age of 30, a negative ultrasound is enough to rule out ADPKD; however, at younger age, an MRI is needed to exclude the disease.

Genetic Testing

- Although genetic testing is not always necessary to make a diagnosis, it can be pretty useful in instances where a definitive diagnosis is needed, in reproductive counseling, early severe forms of PKD, syndromic PKD patterns and/or imaging studies are inconclusive.

- Young patients who will have access to new and available effective disease-modifying therapies would benefit from genetic testing to help confirm their diagnosis before initiating targeted treatment.
- Direct mutation (molecular) screening by Sanger sequencing of PKD1 and PKD2 genes is currently the most common method being used for the diagnosis of ADPKD, followed by multiplex-dependent probe amplification (MLPA). MLPA is used in cases with negative DNA sequencing results [16]. Although genetic testing has been proven to be helpful, it still is expensive, and its interpretation often challenging to understand and implement. With PKD1 and PKD2 genes, there have been more than 1270, and 200 pathogenic mutations reported, respectively proving what a challenge interpretation could pose. Routine ultrasound or genetic screening test for at-risk asymptomatic family members is not recommended.

Differential Diagnosis

- The diagnosis of ADPKD is not difficult when there is an established family history of the disease; But, when that is absent, or presence of findings suggestive of other genetic diseases, the possibility of an alternative renal cystic illness must be excluded, and the differential diagnosis should be broadened.
- Acquired cystic kidney disease with renal dysfunction typically exhibits shrunken kidneys.
- Medullary cystic kidney disease (MCKD) is characterized by late onset of renal cysts that are confined to the corticomedullary junction or renal medulla with relatively normal–sized smooth-contoured kidneys. Medullary sponge kidney (MSK) can also be distinguished from ADPKD by the medullary location of the cysts and dilatation of the collecting duct system [17].
- Solid renal nodules are uncommon in ADPKD, but it is frequently seen in patients with Von Hippel–Lindau (VHL) syndrome and in tuberous sclerosis.
- Other causes of cystic kidneys must be excluded, like multilocular cystic nephroma, haemangioma, Angiomyolipomas, and renal cell carcinoma. The presence of extrarenal manifestations, such as hepatic cysts, can be a helpful clue for diagnosing ADPKD.

Treatment options [18]:

Non-pharmacological: Besides the need for optimal blood pressure control, there are some reno-protective measures to take place early in the disease course, such as regular exercise, diet balance, weight control, smoking cessation, and avoidance of any nephrotoxic agents like aminoglycosides and NSAIDs. Alcohol, caffeine, and estrogen intake should be restricted and quantified, as it was found that both can induce growth of the cysts. Salt restriction, as well as adequate hydration can prevent disease progression by suppressing vasopressin and reducing risk of kidney stones.

Strict blood pressure control: The first-line antihypertensive agents recommended in such cases are those blocking the Renin-Angiotensin-Aldosterone System (RAAS), such as ACEIs and ARBs, which are also considered anti-proteinuric. They both reduce the renal vascular resistance as well as minimize the annual decline in the estimated glomerular filtration rate (eGFR). The aim is to maintain BP of less than or equal to130/80 mmHg.

Chronic kidney disease: By preventing, reduce and treat CKD related complications. Anemia is not often an early problem in CKD-ADPKD patients as compared to other causes of CKD; that's because of the further erythropoietin production by cells surrounding the cysts.

Other treatment modalities: Although there is no definitive specific therapy available at present for ADPKD, numerous medications are being studied, including:

- **Vasopressin V2 receptor antagonism** (Tolvaptan): It slows the GFR decline rate as well as lowers the total kidney volume increase (TKV).
- **HMG- CoA reductase inhibitors**: pravastatin slows the ht-TKV growth rate.
- **Somatostatin analogs**: lanreotide slows the expansion of TKV and the decline of GFR by binding to somatostatin receptors 1–5, which inhibit fluid secretion and cell proliferation [19]. Their use is restricted due to overt adverse effects like GIT upsets, frequent diarrhea, abdominal pain, flatulence, Gall bladder stones, breakthrough hyperglycaemic episodes. Also, it is reported that Octreotide can increase the risk of hepatic cyst infection in the ADPKD. Current clinical trials of DIPAK1 (Developing Interventions to Halt Progression of ADPKD 1) and LIPS (Lanreotide in Polycystic kidney disease Study) evaluate lanreotide's efficacy in slowing the progression of polycystic kidney disease.
- **Antiproliferative drugs**: mTOR and tyrosine kinase inhibitors have not yet been established, likely due to the narrow therapeutic index.
- mTOR inhibitors: Everolimus, Sirolimus and Rapamycin [20].
- Tyrosine kinase inhibitor: bosutinib improves the TKV with no effects on eGFR.
- **Novel strategies still under trial include:**
- Glucosylceramide synthase inhibitors: It blocks the cytogenesis in PKD rats, but in human beings is not approved as yet.
- Oligonucleotides are targeting microRNAs: reduced cyst growth by inhibiting MicroRNA-17 in different PKD mouse models. MicroRNA-17 is the proliferative stimulant.
- In the near future, multidrug therapy will be recommended to target a specific proliferative pathway as well as block cyst inflammatory process and fluid secretion.

Role of Surgery: Large-volume surgical cyst reduction does not affect long-term outcomes. However, selected procedures like aspiration and sclerosis of severely symptomatic renal or hepatic cysts can provide relief. The interventional procedures in ADPKD include the following:

- Per-cutaneous cystic drainage under guide ultrasound provides recovery in refractory cysts that resistant to antibiotic
- Fiberoptic-guided or open surgical drainage of the cysts is also another alternative procedure.
- Kidney transplantation is the best choice for end-stage renal disease patients, as it has cost-efficiency and improves the quality of life with a higher survival rate.
- Nephrectomy (Unilateral or Bilateral): is the last step to be undertaken, and it is indicated in patients with severe, intractable pain, recurrent urinary tract sepsis, inoperable, deep cysts that are difficult to access, or suspected a non-benign lesion, and to provide space for the transplantation.
- In patients with massive hepatomegaly and polycystic liver, surgical intervention is always necessary for forms of either partial hepatectomy or laparoscopic liver cyst unroofing. However, in those with portal hypertension and inoperable severe cystic liver disease, liver transplantation is the best choice.

Cyst Growth and Disease Monitoring:

In the early stages, the disease and cyst expansion develops gradually with no overt decline in kidney function, that makes eGFR a useless monitoring tool. However, ht-TKV is better to use for monitoring as well as prognostication purposes. As a patient is getting older, the decline rate in eGFR becomes clearer with an average rate 6 ml/min per year [21]. The growth rate of the cysts is similar in both PKD1 and PKD2 mutations.

Family planning of pregnancy:

The risk of inheritance of ADPKD to the offspring, as well as the fetal and maternal complications during pregnancy, should be discussed in detail with parents, especially in women who are exposed to oestrogen or progesterone. Genetic testing has been used to implant healthy embryos created by in vitro fertilization. Because most of the antihypertensives has teratogenic effect; thus, the treatment options must be adjusted. Pregnancy-induced hypertension and preeclampsia are common in ADPKD pregnant women, and it requires referral to the expertise of obstetricians [22]. All ADPKD patients and their close family members should be counseled regarding the mode of inheritance; however, routine screening for relatives and asymptomatic adults at risk for ADPKD is not advised.

Prognosis:

At present, without proven therapies to slow cyst growth, half of the ADPKD1 patients end up with ESRD by age 60, which require renal replacement therapy with an overall better prognosis than in the general population. However, those with ADPKD2 or atypical PKD patterns might never require kidney replacement therapy (KRT). Although post- transplant complications are commonly seen, kidney transplantation is still the best KRT with the best outcomes [23]. A dialysis is an option; bear in mind hemodialysis is superior to peritoneal dialysis because, PD has reported more complications like abdominal wall hernias and peritonitis secondary to infected cysts. At the same time, hemodialysis showed a higher survival rate, polycythemia, and less risk for developing RCC. Appropriate candidates for renal transplantation should be identified and evaluated early, anticipating their need for renal replacement therapy to minimize or entirely avoid time spent on dialysis.

Mortality in ADPKD

A retrospective study from the United Kingdom had shown the age-specific death rate for those diagnosed with ADPKD ranged from 37 to 82 years of age, with a median of 61. Amongst the significant causes of death in the study, cardiovascular causes comprised the most at over two-fifths of the deaths. Sepsis followed with just under one-sixth of the deaths. Neurological disorders and Uremia each contributed just under one-eighth of the causes of death [24].

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Part 2: A submission ready manuscript.

Review the clinical presentation and outcome of autosomal dominant polycystic kidney disease attending Inkosi Albert Luthuli Central Hospital, in KwaZulu Natal, South Africa during the period from 2013-2017. A retrospective 5-year review.

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Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. The prevalence is not well described, and literature is scarce regarding ADPKD in sub-Saharan Africa. We aimed to review the demographics, clinical profile, and treatment outcome among ADPKD patients.

Methods: A retrospective review of 81 ADPKD subjects was conducted at Inkosi Albert Luthuli Central Hospital (IALCH) from January 2013 to December 2017. Ravine's ultrasonographic criteria established the diagnosis. Clinical data were captured from medical records. The development of end-stage renal disease, need for renal replacement therapy, transplantation, nephrectomy, and death were specified outcomes.

Results: Females predominant, male: female ratio (1:1.4) with a median age of 55 years. Indians were more prevalent (44.0%). Hypertension was present in 95.1%, and abdominal pain was the most frequent presenting complaint (28.4%). Haematuria was prevalent in 22.9%, and only four patients had UTIs with no gender predilection. Approximately 57% of patients were not anemic, with hemoglobin above 11 g/dL. A liver cyst was the predominant extra-renal manifestation. Significant proteinuria and raised CRP were seen in end-stage renal disease (ESRD) patients on kidney replacement therapy (KRT). ESRD and KRT occurred in 42.0% of patients. Nephrectomy and kidney transplantation were rare (6.2%).

Conclusion: The clinical profiles and outcomes were comparable to other literature elsewhere. Females were predominant. Further studies are required to determine the best novel medical treatment in Sub-Saharan Africa with the impact of HIV infection. Screening testing of ADPKD relatives is highly recommended.

Keywords: Autosomal dominant polycystic kidney disease; KwaZulu-Natal; Clinical presentation, Outcome.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease with two identified genetic defects, PKD1 and PKD2. Both genders are affected equally; however, males might have a more severe phenotype (1). Hypertension is prevalent even in the early stages of the disease. Furthermore, kidney function declines gradually, and ESRD occurs in only 5-10% of ADPKD subjects. Caffeine, alcohol, and estrogen therapy can progress renal cystic development (2). Polycystic liver and cerebral aneurysms are the most typical and extra-renal severe manifestations. Proteinuria is often subnephrotic in ADPKD and is considered a prognostic tool (3).

Ravine's criteria for ADPKD can be established on an ultrasound basis, CT scan, or MRI. The presence of bilateral enlarged multicystic kidneys is the characteristic radiological feature of ADPKD (4). Based on randomized trials, novel tolvaptan is now Food and Drug Administration (FDA) approved a treatment in those ADPKD patients whose kidney function decline is rapidly worsening. Reno-protection strategies such as blood pressure control, avoidance of the risk factors and nephrotoxic agents remain the mainstay of treatment. Literature is scarce regarding ADPKD in the region of sub-Saharan Africa. The aim is to review the demographic distribution and clinical profile with treatment outcomes in ADPKD in the South African context at KZN tertiary hospital (IALCH).

Methods

This study was a retrospective chart review of ADPKD databases of 81 patients 18 years, and older referred to IALCH from January 2013 to December 2017.

Data collected include demographics and clinical laboratory information with treatment outcomes detailed in tables 1 and 2.

Blood pressure (BP) was classified as hypertensive, normotensive, or hypotensive, according to South African Hypertension Society (SAHS). BP of 90/60 mmHg and below is hypotension. Whereas 140/90 mmHg or above is considered to be hypertension. Normotensive is defined as BP of 120/80 mmHg. However, high normal BP is defined as 130-139 over 85-89 mmHg

The diagnostic ultrasonic Ravine's criteria were applied to the majority of patients. However, few cases were diagnosed by modified Pei-Ravine's criteria using CT and MRI.

The duration of illness, including the date of the first and last visit, was analyzed and concluded in this study.

The biochemical data of creatinine and glomerular filtration rate (eGFR) were analyzed in Table 5. Glomerular filtration rate (GFR) was estimated using the MDRD equation. eGFR of 60 mL/min/1.73m2 or higher is in the normal range, while the ones of <15 mL/min/1.73m2 is deemed to be ESRD. Estimated GFR values between 59 and 15 imply variable degrees of kidney disease.

MDRD eGFR (mL/min/1.73 m2) =

$$175 \times (\text{Scr in } \mu\text{mol/L} / 88.4)^{-1.154} \times (\text{Age in years})^{-0.203} \times (0.742 \text{ [if female]})$$

Patients under 18 and those diagnosed with ADPKD are doubtful, or electronic data sets that cannot be retrieved were all excluded from the study.

Ethical approval was granted by the University of KwaZulu Natal's Human Research Ethics Committee (ref. no. BE081/19).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 27.0.
Categorical variables were described as numbers and percentages and compared using the Chi-square test, Fisher's exact test, or Fisher-Freeman-Halton exact test, where appropriate.
Continuous variables were analyzed using the Kolmogorov-Smirnov test for normality. As many continuous variables had a non-Gaussian distribution, all continuous variables were described using the median and interquartile range (IQR) and compared using the Mann-Whitney U-test or related-samples Wilcoxon Signed Rank test, as appropriate. A p-value of <0.05 was deemed statistically significant.

Results

A total of 81 patients were diagnosed with ADPKD at IALCH during the period from January 2013 to December 2017. The baseline demographic data and comorbidities of the cohort are shown in Table 1. The median age was 55 years (IQR 47-62 years), with the youngest patient being 26 years old and the oldest 78 years old. The median age (IQR) was 53 (45-60) years in patients with a duration of illness of fewer than five years, 56 (43-61) years in those with a period of 5-10 years, and 60 (51-67) in those with a period of more than ten years; this was however not statistically significant, p=0.153. Only 3 (3.7%) patients had no known comorbidities, while 39 (48.1%) had more than one comorbid condition. The category of "other" comorbidities included gout, pituitary macroadenoma, systemic lupus erythematosus, and psoriasis. Of the patients with HIV, all eight were on antiretroviral therapy (ART), and the CD4 count was above 200 cells/ul in 7 and unknown in 1.

Table 1: baseline demographic data and comorbidities		
		n (%)
Age	<40	10 (12.3%)
	40-60	44 (54.3%)
	>60	27 (33.3%)
Gender	Male	34 (42.0%)
	Female	47 (58.0%)
Race	Indian	36 (44.4%)
	Black	34 (42.0%)
	Coloured	3 (3.7%)
	White	8 (9.9%)
Comorbidities	Anaemia	4 (4.9%)

	Cerebrovascular disease	4 (4.9%)
	Diabetes	13 (16.0%)
	Dyslipidaemia	10 (12.3%)
	HIV	8 (9.9%)
	Hypertension	77 (95.1%)
	Malignancy	3 (3.7%)
	Osteoporosis	4 (4.9%)
	Thyroid disease	4 (4.9%)
	Other	11 (13.6%)

Clinical data related to the ADPKD is presented in Table 2. In 33 patients (40.7%), ADPKD was diagnosed incidentally in patients who presented to a healthcare facility for another unrelated condition. The other 48 (59.3%) patients presented with clinical features that were deemed likely to be related to ADPKD. These presenting features are highlighted in Table 2. 34 (42.0%) patients had extra-renal manifestations of ADPKD: polycystic liver disease noted in 33 patients and cerebral aneurysms in one patient. On first presentation 43 (53.1%) patients were normotensive, 36 (44.4%) were hypertensive and 2 (2.5%) were hypotensive. At the last recorded clinic visit, 42 (51.9%) were normotensive, 35 (43.2%) hypertensive, and 4 (4.9%) hypotensive.

The outcome of the patients (as of their last clinic visit) is also shown in Table 2. While 34 (42.0%) patients received kidney replacement therapy for ESRD secondary to ADPKD, an additional patient received continuous renal replacement therapy (CRRT) during critical care for an unrelated condition. While the renal dysfunction from the ADPKD likely contributed to the need for CRRT, as this was not chronic dialysis for ESRD, it was not included in the total number of patients receiving dialysis. Of the 34 patients who received renal replacement therapy, 7 (20.6%) received peritoneal dialysis, while the remaining patients required hemodialysis.

Of the two patients who died, both were male. One died of acute myocardial infarction, and one died of an unknown cause.

Table 2: Clinical and outcome data		
		n (%)
Presentation	Incidental finding	33 (40.7%)
	Abdominal pain/back pain	23 (28.4%)
	Dysuria	3 (3.7%)

	Gastrointestinal disturbance	3 (3.7%)
	Lower limb pain	3 (3.7%)
	Swelling of lower limbs/body	13 (16.0%)
	Weakness	2 (2.5%)
	Other	3 (3.7%)
Extra-renal manifestation/s		34 (42.0%)
Duration of follow up (from initial to last recorded clinic visit)	<5 years	50 (61.7%)
	5-10 years	18 (22.2%)
	10-15 years	13 (16.0%)
	>15 years	0 (0.0%)
Outcome	ESRD	34 (42.0%)
	Kenal replacement therapy	34 (42.0%)
	Cyst decortication or Aspiration	0 (0.0%)
	Nephrectomy	5 (6.2%)
	Kidney transplantation	5 (6.2%)
	Death	2 (2.5%)

Imaging data is included in Table 3. The kidney length ranged from 9cm to 21cm on the right and 9cm to 22cm on the left. The liver span ranged from 14 to 22cm. The diagnosis of ADPKD was made on imaging criteria in all patients. In two patients, polycystic kidneys were noted as an incidental finding on MRI. No patients received renal biopsies or genetic testing. In the five patients who had nephrectomies, the following results were reported: invasive renal cell carcinoma in 2 patients and hemorrhagic cysts with thrombus in patients. No macroscopic or histological findings were available for the 5th patient.

Table 3: Imaging data

		Median (IQR) or n (%)
Ultrasound Right kidney	Normal	0 (0.0%)
	Normal size but cystic	8 (10.1%)
	Enlarged and cystic	70 (88.6%)
	Nephrectomy/absent	0 (0.0%)
	Transplant kidney	1 (1.3%)

Ultrasound Left kidney	Normal	0 (0.0%)
	Normal size but cystic	6 (7.5%)
	Enlarged and cystic	71 (88.8%)
	Nephrectomy/absent	2 (2.5%)
	Transplant kidney	1 (1.3%)
Ultrasound liver	Normal	37 (52.9%)
	Cystic	33 (47.1%)
CT abdomen: compatible with ADPKD	Yes	23 (100.0%)
	No	0 (0.0%)
MRI abdomen: compatible with ADPKD	Yes	2 (100.0%)
	No	0
Right kidney length on ultrasound(cm)		16 (13.00 - 18.00)
Left kidney length on ultrasound(cm)		16 (14.00 - 19.00)
Liver span on ultrasound(cm)		18 (17.00 - 19.00)

Urinalysis data is shown in Table 4, and biochemical data in Table 5. Unless otherwise stated, the data presented is the first result available. Concerning creatinine, 54 (66.7%) had an increase in creatinine, 24 (29.6%) showed a reduction in creatinine, and 3 (3.7%) had an unchanged creatinine. In terms of the association with KRT, no patient with an unchanged creatinine received RRT, 17 (31.5%) with an increase in creatinine received KRT, $p<0.001$.

Of the three patients with random blood glucose greater than 11.1 mmol/l, all three had an HbA1C greater than or equal to 6.5%. Of the 15 patients who had an elevated HbA1c, seven patients were known to be diabetics. Thus, a total of 21 patients (25.9%) were diabetics.

Table 4: Urinalysis data

		Median (IQR) or n (%)	**Minimum**	**Maximum**
Urine microscopy and culture	Negative	43 (91.5%)		
	Positive	4 (8.5%)		
Urine dipstick protein	Absent	48 (69.6%)		
	Present	21 (30.4%)		
Urine dipstick red blood	Absent	54 (77.1%)		

cells	Present	16 (22.9%)		
Urine protein:creatinine ratio (g/mmol)	<0.015	0 (0%)		
	0.015-0.049	7 (14.9%)		
	0.05-0.099	11 (23.4%		
	0.1-0.3	8 (17.0%)		
	>0.35	21 (44.7%)		
Urine protein:creatinine ratio (g/mmol)		0.21 (0.07 - 0.76)	0.02	1.680

Table 5: Biochemical data

		Median (IQR) or n (%)	**Minimum**	**Maximum**
Urea (mmol/L): **First visit**	Normal	37 (45.7%)		
	Elevated	44 (54.3%)		
Urea (mmol/L): **Last visit**	Normal	17 (21.0%)		
	Elevated	64 (79.0%)		
Creatinine (umol/L): **first visit**	Normal	37 (45.7%)		
	Elevated	44 (54.3%)		
Creatinine (umol/L): **Last visit**	Normal	24 (29.6%)		
	Elevated	57 (70.4%)		
eGFR (mL/min/1.73 m^2**): First visit**	Normal	25 (35.2%)		
	Reduced	46 (64.8%)		
eGFR (mL/min/1.73 m^2): **Last visit**	Normal	17 (21.8%)		
	Reduced	61 (78.2%)		
Haemoglobin (g/dL)	>11 g/dL	46 (56.8%)		
	11-7 g/dL	26 (32.1%)		
	<7 g/dL	9 (11.1%)		
CRP (mg/L)	<10 mg/L	28 (50.9%)		
	>/= 10 mg/L	27 (49.1%)		
Random blood glucose (mmol/L)	<5.6mmo/l	44 (58.7%)		
	5.6-11.0	28 (37.3%)		

	mmol/l			
	>11.0 mmol/l	3 (4.0%)		
HbA1C (%)	<6.5%	20 (57.1%)		
	>/= 6.5%	15 (42.9%)		
Urea (mmol/L): **First visit**		7.6 (5.30 - 20.00)	2.5	65.1
Urea (mmol/L): **Last visit**		11.8 (8.00 - 18.00)	3.4	53
Creatinine (umol/L): **first visit**		135 (82.00 - 441.00)	39	1549
Creatinine (umol/L): **Last visit**		271 (98.00 - 494.00)	14	1343
eGFR (mL/min/1.73 m^2): **First visit**		32 (9.00 - 60.00)	2	118
eGFR (mL/min/1.73 m^2): **Last visit**		17 (8.00 - 51.00)	1	118
iGFR (mL/min) (n=45)		58 (33.00 - 85.00)	1	126
Haemoglobin (g/dL)		11.5 (9.10 - 13.10)	5.4	17.7
CRP (mg/L)		9 (3.30 - 48.00)	0	391
Random blood glucose (mmol/L)		5.2 (4.60 - 6.10)	4	22.9
HbA1C (%)		6.2 (5.50 - 7.50)	5.3	11.9

There was no significant association (at $p < 0.05$ threshold, using Chi-squared test) between demographics, comorbidities, clinical data and outcome, and the presence or absence of liver cysts. The development of ESRD is a key outcome in patients with ADPKD. Table 6 compares the results of the parameters presented above in patients with and without ESRD.

Table 6: Variables with significant associations with ESRD (excluding urea, creatinine and GFR)				
		ESRD	**No ESRD**	
		Median (IQR) or n (%)	Median (IQR) or n (%)	p-value
Osteoporosis		4 (11.8%)	0 (0.0%)	0.028
Duration of follow up	<5 years	27 (79.4%)	23 (48.9%)	0.019
	5-10 years	5 (14.7%)	13 (27.7%)	

	10-15 years	2 (5.9%)	11 (23.4%)	
	>15 years	0 (0.0%)	0 (0.0%)	
Urine microscopy and culture	Positive	4 (20.0%)	0 (0.0%)	0.027
Urine dipstick protein	Present	12 (52.2%)	9 (19.6%)	0.006
Urine dipstick red blood cells	Present	10 (41.7%)	6 (13.0%)	0.007
Urine protein to creatinine ratio (g/mmol)	<0.015 g/mmol	0 (0.0%)	0 (0.0%)	0.036
	0.015-0.049 g/mmol	3 (15.0%)	4 (14.8%)	
	0.05-0.099 g/mmol	1 (5.0%)	10 (37.0%)	
	0.1-0.3 g/mmol	3 (15.0%)	5 (18.5%)	
	>0.3 g/mmol	13 (65.0%)	8 (29.6%)	
Haemoglobin (g/dL)	>11	11 (32.4%)	35 (74.5%)	<0.001
	11-7	17 (50.0%)	9 (19.1%)	
	<7	6 (17.6%)	3 (6.4%)	
CRP (mg/L)	>/= 10mg/L	19 (67.9%)	8 (29.6%)	0.005
Urine protein to creatinine ratio (g/mmol)		0.59 (0.20 - 1.72)	0.09 (0.06 - 0.46)	0.027
Haemoglobin (g/dL)		9.2 (7.30 - 12.10)	12.2 (11.10 - 13.30)	<0.001
CRP (mg/L)		28 (7.50 - 82.00)	5.8 (1.60 - 14.00)	0.002

Discussion

Females were predominant (58.0%) in this study and the median age of the cohort was 55 years, comparable to what was described by Chijioke, et al. [5]. Male gender was, however, more prevalent in the study by Arogundade, et al. [6]. Most patients in this study were in the 4th to 6th decade of life (54%), with most (62%) having a duration of less than 5 years. This is older than the 3rd and 4th decades as previously reported (6). This may be due to differences in referral patterns and is difficult to

compare accurately between studies. The largest proportion of ADPKD patients in this study were Indian (44%), followed by Black African patients (42%) and White patients (10%). This differs somewhat from the demographic findings of a previous study done at IALCH comparing urban and rural patients with chronic kidney disease of any aetiology which showed that in urban patient, Black African patients were most frequent at 50%, followed by Indian patients at 42% and White patients at 6% [7]. According to Stats SA and Census 2011, the eThekwini Metro has the following population demographics: Black African 74%, Indian 17%, White 7%. It is thus not clear if these observed differences reflect differences in the referral pathway or other, unidentified covariates. There is a suggestion that this may be more than just the referral pathway as the demographic profile differs from that of all patients presenting with CKD and from the demographic profile of eThekwini Metro.

In terms of the pattern of clinical presentation, out of the symptomatic patients, abdominal pain and backache were the main presenting complaints in our study (28.4%) which is lower than the 60.0% reported by Bajwa et al. [8]. Abdominal pain is usually due to mass effects, renal stones, cystic hemorrhage, and urinary tract infections (UTIs). In this study, 8.5% had UTIs, lower than the 35% quoted by Romao et al. [9]. Around 60.0% of ADPKD patients develop micro- or macroscopic haematuria, most often due to UTIs [10]. In this study, the results were inconsistent with the literature, and microscopic hematuria was prevalent in only 22.9% of whom underwent the test. UTI was equally dominant in males and females with no gender preference, which is not in conformity with findings by Sklar et al. [11]. More than half of the subjects (56.8%) were not anemic and had hemoglobin greater than 11 g/dL, which may be accounted for by increased erythropoiesis secondary to excess cystic production of erythropoietin [12].

Hypertension was highly prevalent in this study, 95.1%. It was higher than 73% quoted by Alves et al. [13]. That is inconsistent to the study done in Congo by Assounga et al [14], where only 7% were found to be hypertensives. The evidence shows that hypertension can occur at an earlier age in ADPKD compared to the general population (6), approximately 80.0% before the significant decline of renal function and up to 100% in that ADPKD with ESRD [15]. This was inconsistent with our study, where 87.6% of patients were over 40 years at presentation, probably due to delayed referrals, as seen in Table 1.

Extra-renal manifestations occurred in 42.0% of the study population. Polycystic liver disease ranked as the commonest extra-renal manifestation and accounted for 97% of extrarenal manifestations in our study. Polycystic liver disease can occur in more than 80.0% of ADPKD patients [16]. However, a lower incidence of 10.4% was quoted by Alves et al. in Brazil among elderly subjects. The occurrence of hepatic cysts was higher among females in this study, similar to what was previously reported by

other authors [11]. The prevalence of polycystic liver disease in our cohort was in the middle of this range, at 47.1% in patients with a liver ultrasound. Intracerebral aneurysms (ICA) generally occur in 10% of ADPKD patients compared to 2.5% in the general population [17]. Here, our study found the occurrence rate of ICA at (3.0%) based on CT scans and MRI, which was similar to what was quoted by Chapman AB et al. [18]. The reliability of this finding is limited by the fact that neuroimaging was not conducted routinely. There was no evidence of the other extra-renal manifestations in our subjects. At least 50 patients (61.7%) of the total cohort had a duration of follow up of fewer than five years. The prevalence of the < 5 years duration of illness is 79.4% in the ESRD group compared to 48.9% of those without ESRD. This could be due to the genotype-phenotype of ADPKD, which has a variable degree of progression to ESRD. Those with ESRD seemed to have early referrals, whereas those without ESRD were likely deemed more stable and managed at their regional hospitals. This was consistent with the literature [19].

For those with a tentative diagnosis of ADPKD and who don't fulfill Ravine's criteria, DNA-based testing must be conducted [20]. However, genetic analysis was unavailable for any patient in our study because all were diagnosed on imaging.

The treatment modality of ADPKD patients in this study sample indicates that none of the subjects received cysts decortication or aspiration. In contrast, only five patients (6.2%) had a nephrectomy, and same number of patients underwent kidney transplantation. Forty-two percent had KRT with predominantly hemodialysis (79.4%). Peritoneal dialysis (PD) is also used (20.6%) in our population and may have better survival in ADPKD patients [4]. In resource-poor settings, however, hemodialysis may be the preferred option due to the scarcity of PD fluids and associated high costs and complications.

Thirteen patients had a history of diabetes mellitus (DM). Regarding testing, only 3 had a diabetic range of random blood glucose (RBS). While at least 15 patients had HbA1C values of greater than 6.5%, suggesting they had diabetes [21]. But there may be more because we only tested 35 subjects out of the 81. There were no patients with HbA1C less than 6.5% that had an RBS above or equal to 11.1 mmol/l. Based on history and testing, a combined prevalence of diabetes of 25.9% was noted.

The CRP was significantly elevated between ESRD (67.9%) and non-ESRD subjects (29.6%). That could be attributed to the inflammatory reactions to fistulae, dialysis catheters, bioincompatible dialysis membranes, dialysate, and malnutrition. This was compatible with the literature findings by Stenvinkel P et al. [22].

Nephrotic range proteinuria was present in 44.7% of the cohort, occurring in 65.0% of patients with ESRD and 29.6% without ESRD. Nephrotic range proteinuria has previously been uncommon in

ADPKD; the high prevalence in our cohort could reflect coexistent nephropathy from diabetes, as it was prevalent in the ESRD group [23]. That was parallel to the results of a review where the frequency of proteinuria was assessed qualitatively and ranged in non-uremic adults from 34.0% to 80.0% in adults with advanced renal failure [24].

The mortality rate was (2.5%) in our study, which is comparable to the figure reported by Chijioke et al. [5]. Death was higher among males, similar to other authors [25]. Uremia, rupture ICA, cardiac diseases, and sepsis are commonly associated with mortality in ADPKD [5]. That's consistent with our study, where one had a fatal myocardial infarction.

Limitations of this study

This study has potential limitations. A retrospective review of electronic data, where only data captured could be analyzed. The small sample size at a single center with possible missing data may lead to bias and difficulty in determining any associations. There is a possibility of overestimation as the study was conducted at a tertiary hospital in a specialized department, which may have resulted in referral bias. There may also have been patients with ADPKD who may have been missed because they were asymptomatic.

Conclusion

This study reports on the demographics, clinical picture, and outcomes of 81 patients presenting to a single renal unit in Durban, South Africa. The study noted an unusual demographic profile with a female predominance and Indian patients representing the most common race group. The clinical profile and outcome were broadly similar to other cohorts; however, a high-rate nephrotic range proteinuria was noted which warrants further investigation. Blood pressure monitoring is required in all ADPKD patients, even without detectable changes in GFR. Screening of family members should be recommended and is necessary for early diagnosis and management to delay the progression to ESRD. There is a need for further studies to determine the best novel medical therapy in the region of Sub-Saharan Africa, particularly with the impact of HIV infection.

Conflict of interest

No conflict of interest to declare

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Appendices

Appendix 1:

The final Study Protocol

Research Protocol: MMed (internal medicine)

Student: Dr. TAHA ABULGHASM

Student number: 215082415

Supervisor: Professor Alain Guy Honoré Assounga

- Doctor of Medicine (MD); Université Marien Ngouabi (Congo-Brazzaville)
- Certificate of Special Studies (CES) French National Board in internal medicine and Nephrology, University of Montpellie (France) 30-06-1988
- Master of Science (MS)in Mathematics (Combinatorics) Northeastern University
- (Boston, USA) 1993 Doctor of Philosophy (PhD) in Immunology. Northeastern University (Boston, USA) 1993.
- Intern, General Hospital of Brazzaville, Congo 1983-84
- Residency and Fellowship in Internal Medicine and Nephrology CHU de Montpellier, France 1984-1988
- Research Fellow, in Medicine, Nephrology Division, Beth Israel Hospital and Harvard Medical School, Boston, MA, USA 1988-1990.
- PhD in Immunology and Molecular Biology, Northeastern University, Boston, MA, USA; and Lecturer in Immunology 1990-1993.
- Consultant Nephrologist, Brazzaville's University Hospital, Congo-Brazzaville 1993-1997.
- Consultant Physician/Nephrologist Princess Marina Hospital, Gaborone, Botswana 1997-2000.
- Principal Specialist/ Head of Nephrology Inkosi Albert Luthuli Hospital 2001-2005.
- Kwazulu-Natal Dept of Health Chief specialist, Head of Dept of Nephrology, Univ. KwaZulu-Natal 2006.

Title of study

Review the clinical profile and outcome of autosomal dominant polycystic kidney disease attending Inkosi Albert Luthuli Central Hospital, Nephrology in Durban, KwaZulu Natal, South Africa during the period from 2013 - 2017.

2.2 Identify the problem that is motivating your research.

Autosomal dominant polycystic kidney disease is one of the commonest life threatening, multisystem

genetic disease that affects >12.5 million people world- wide. ADPKD is characterized by bilateral renal cysts, leading to gross kidney enlargement and end-stage renal disease that requires dialysis or transplantation. Patients with ADPKD may also develop hepatic and pancreatic cysts, hypertension, and intracranial aneurysms.

ADPKD is due to mutations in Pkd1 or Pkd2 genes. Pkd2 form a biochemical complex with Pkd1. ADPKD is an untreatable disease due to a gap in understanding the biochemical, structural, and functional properties of Pkd1, Pkd2, and the Pkd1/ Pkd2 complex, which impedes the development of therapeutic strategies.

Current treatments only symptomatic without altering disease progression

2.3 What is the research question or the hypothesis?

Autosomal dominant polycystic kidney disease demographic records, disease spectrum, radiological findings and clinical features and outcome in Inkosi Albert Luthuli central Hospital are quite similar to what has been described in the international data.

The aim of this study?

To investigate and review the demographic distribution, clinical presentation, radiological profile, and the treatment outcome of autosomal dominant polycystic kidney disease in South African context.

The objectives of the study.

- To determine the clinical presentation of ADPKD patients that presented to IALCH.
- To examine the demographic profile of the study participants.
- To review the specific renal and extra-renal ultrasonic patterns of ADPKD.
- To assess radiographic and sonographic finding of patients with ADPKD.
- To assess the outcomes of management modalities and the therapies that patients were placed on.
- To determine if there is any association with other co-morbidities (HIV, DM, HTN).

Background and Literature review

PKD can be inherited as an autosomal dominant trait (ADPKD) or an autosomal recessive trait (ARPKD). It is the most frequent genetic cause of renal failure in adults, manifested with focal microdissected cystic kidneys or mixed renal and extra-renal [1]. ADPKD commonly occurs worldwide in both children and adults of all ethnic groups with more disease progressive in men than in women in an incidence of more than 1:500, whereas ARPKD is uncommon and occurs primarily in neonates and children [2]. Each child of an affected parent has a 50% chance of inheriting the mutated gene, which is completely penetrant meaning that virtually 100% of individuals who inherit a mutated PKD gene will develop renal cysts that can be detected sonographically by age 30. The disease arises as a spontaneous

mutation in approximately 5% of cases. Abnormalities in gene expression, cell polarity, fluid secretion, apoptosis, and extracellular matrix have also been described in PKD, but the mechanism of cyst formation remains incompletely understood [3,4-5]. ADPKD is caused by mutations of either the PKD1 gene on chromosome 16 or the PKD2 gene on chromosome 4.

The clinical picture includes pain—in the abdomen, flank, or back—which is the most common initial complaint, and it is almost universally present in patients with ADPKD. Dull aching and an uncomfortable sensation of heaviness and abdominal mass may result from a large polycystic liver. Also, patient might present with urinary symptoms of dysuria, hematuria, urgency, and frequency. It typically present in the third and fourth decade of age. Progressive ESRD usually occurs within 5 to 10 years after the development of renal insufficiency [6]. It is usually complicated by hemorrhage, infection, nephrolithiasis, and intractable pain. Systemic hypertension is one of the most common early manifestations in which increased diastolic BP is the rule, occurring in more than 70% of patients. It's attributed to activation of the renin-angiotensin system [7-8]. ADPKD is regarded as a systemic disease and the genes responsible are widely expressed, and mutations can affect a variety of extrarenal tissues [9]. Cysts can arise in the liver (75% of patients), pancreas (rare), ovaries, and choroid plexus. The hepatic cysts doesn't cause liver failure, but its enlargement produce mass effects. Other extrarenal manifestations include cerebral and aortic aneurysms, colonic diverticula, and cardiac valvular abnormalities [10].

The diagnosis is built up on clinical features, laboratory profile, imaging studies and genetic testing. The radiological studies used in evaluation of ADPKD include Ultrasonography diagnostic criteria of at least 2 cysts in 1 kidney or 1 2, 4 cysts in each kidney in an at-risk patient of age 30, 45, 60 respectively, is the technique of choice to make a diagnosis [11]. CT-scanning, MRI and MRA are not routinely used, only in complicated cases such as suspected renal tumor, monitor kidney size and in ADPKD-related intracranial aneurysms [12]. In addition, renal cysts arise from all segments of the nephron and the renal collecting system that has undergone somatic mutation of the PKD1 and PKD2 genes, which have been identified in the cells lining the cysts in both the kidney and liver. However, the severity of the disease, the age of onset of ESRD, and the spectrum of extrarenal manifestations vary widely between affected individuals, even within the same family [13]. Possible explanations for the variable expressivity of the disease are mutations in the 5′ end of the gene appear to be associated with earlier onset disease than mutations in the 3′ end. The location of mutations in the gene has been reported to have a nonlinear relationship to clinical severity [14-15].

Management of ADPKD is based on control blood pressure, electrolyte imbalances, good analgesia and optimal fluid rehydration. The role of antibiotics is to treat UTI and prevent cardiac valve infection [16].

The surgical modalities include cystic drainage, open excision, Nephrectomy and/or partial hepatectomy [17].

The prognosis of individuals with ADPKD may live a normal lifespan without knowing that they have the disease. More typically, however, 70% of them would develop renal failure required renal replacement therapy by age 60 year [18].

The presence of more than one of these risk factors (Male sex, Hypertension, Gross hematuria, UTI, PKD1genotype) will provoke the progression to end-stage renal disease (ESRD). Although the 2 forms of ADPKD, ADPKD1 and ADPKD2, share similar clinical features, renal prognosis is strikingly different. ADPKD2 is a milder disease [19].

Conclusion

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders in humans. It is the most frequent genetic cause of renal failure in adults, accounting for 6-8% of patients on dialysis in the United States.

ADPKD is a multisystemic and progressive disorder characterized by the formation and enlargement of cysts in the kidney and other organs (e.g. liver, pancreas, spleen). Clinical features usually begin in the third to fourth decade of life, but cysts may be detectable in childhood and in utero [20] .

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Research design: Retrospective observational descriptive study.

Study population: All adult patients (age > 18yrs), inward and/or out-patients who diagnosed with ADPKD within 2013 - 2017 attending IALCH.

Study sample: All adult patients of 18 year and older who diagnosed with ADPKD at IALCH – Nephrology between January 2013 and December 2017.

Sampling technique: Electronic chart review / purposive sampling.

Sampling strategy: The study population will include All adult patients of 18 year and older who diagnosed with ADPKD at Nephrology department during the period between 01 January 2013 and 31 December /2017.

Variables: Confounding factors that may affect the study outcomes include all these variables:

- Age
- Gender
- Race,
- Duration of symptoms and clinical presentation, including abdominal pain, abdominal distension, hypertension, hematuria, etc.
- RBS / HbA1c
- CRP and ESR level
- USS of kidneys / liver.
- CT-scan features, MRI & MRA.
- Histological / Histopathological findings.
- Medications and treatment modalities
- Outcome post therapy.
- HIV status including CD4 count and Viral Load

Inclusion criteria:

All ADULTS of 18 year and above, all ethnic groups and all gender who is diagnosed with ADPKD at Nephrology department at Inkosi Albert Luthuli Central Hospital during the period between 01 January 2013 and 31 December /2017.

Exclusion criteria:

- Patient underage of 18 year.
- Patient in whom the diagnosis of ADPKD is doubtful.
- Cases where electronic data sets cannot be retrieved.

Data collection methods and Tools:

Research method: data capture sheet

Retrospective electronic chart review between January 2013 and December 2017 in Nephrology department at Inkosi Albert Luthuli Central Hospital, Durban, KZN, South Africa.

Data analysis techniques

Sample size determination: All patients with diagnosed ADPKD seen at Inkosi Albert Luthuli Hospital between 2013 and 2017 will be included in this project. It is estimated that between 60 and 70 individual patients were newly diagnosed in that time period. With a sample of this size, the demographic and clinical characteristics of this population can be estimated to within ± 17% with probability of 95% and assuming a non-informative estimate of 50%. Sample size calculated using Stata V15 statistical software.

Statistical analysis

Descriptive statistics will be used to summarize the data. Frequencies and percent will be used for categorical data, such as gender and symptoms. Frequency distributions of numeric data, such as laboratory results will be examined for normality and means (SD) or medians (IQR) used as appropriate. Subgroup comparisons of demographic and clinical characteristics by outcome (alive/dead) will be done using chi-square or fisher's exact tests for categorical data and t-tests or Mann-Whitney for numeric data. Statistical analysis will be done using Stata V15 statistical software.

Power one proportion .5 .67

Performing iteration...

Estimated sample size for a one-sample proportion test

Score z test. Ho: p = p0 versus Ha: p! = p0

Study parameters:

Alpha = 0.0500 Power = 0.8000 Delta = 0.1700

p0 = 0.5000 Pa = 0.6700

Estimated sample size: N = 66

Study location

The study location will include patients (age 18 years and older) who diagnosed with ADPKD at the Inkosi Albert Luthuli Central Hospital.

Study period

The study population will include Patients who were diagnosed with ADPKD at Nephrology department at Inkosi Albert Luthuli Central Hospital during the period between 01 January 2013 and 31 December /2017.

Limitations of the study

The study is limited to one center. This may not be truly representative of the general population, but as this is the only center that provides this service for the population of Kwazulu-Natal, it is reflective of the state of care for Autosomal Dominant polycystic kidney disease.

Due to a retrospective of the study, incomplete data and lack of follow-up may affect the findings of this study. Inconsistencies in capturing of clinical and laboratory data.

Ethical considerations

As this is a retrospective study with no patient contact informed consent will not be necessary. There will be no direct impact on patient care. No patient identifier will be used, and subjects will be allocated study numbers. A data sheet these with allocations will be kept separating, Confidentiality with all data captured from records will be ensured entering by password protect to the data set

Appendix 2:
The Guidelines for Authorship for the Journal selected for submission of the manuscript

Manuscript preparation

Instructions for Authors

Aim and scope of the Journal

The African Journal of Nephrology (Afr J Nephrol) is the official journal of the African Association of Nephrology (AFRAN) and publishes peer-reviewed papers relating to clinical or basic research in nephrology and hypertension, as well as nephrology education. The Journal considers submissions of original and review articles, case reports, technical reports, practice guidelines, images in nephrology, teaching points, proceedings of national or regional congresses, and letters to the Editor.

General

Manuscripts may only be submitted online, via the Journal website. Manuscripts should not be under consideration by another journal and should not have been published previously except as a poster or abstract. We recommend that manuscripts be scanned with a plagiarism checker before submission. Permission from the copyright holder must be submitted with manuscripts containing previously published material such as figures or tables.

Manuscripts which fail to satisfy the requirements set out in this document may be rejected without further review.

Authors are referred to the uniform requirements for manuscripts submitted to biomedical journals at http://www.icmje.org/.

Language policy

Authors are invited to submit articles written in English or French. All French articles must also be accompanied by an English title, abstract and list of keywords. Please contact us if assistance is required.

Authorship

All authors must have made a significant contribution and must have approved the final manuscript submitted for publication. A signed authorship statement must be submitted by each author to confirm that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Lesser contributions should be indicated in an Acknowledgments paragraph after the Conclusions. Persons mentioned in the Acknowledgments must have agreed to be acknowledged in this way.

Ethics

All studies must comply with institutional and international regulations such as the Declaration of Helsinki. Human and animal studies require ethics committee or institutional review board approval, and human studies require informed consent. Compliance with these requirements must be documented at the end of the Methods section of the manuscript.

Acknowledgements

Manuscripts should include an Acknowledgements section, if appropriate. This follows the Conclusions and should provide detail on funding sources and other contributions to the paper that do not merit authorship.

Conflict of interests

The manuscript and cover letter must include a declaration that the authors have no conflict of interests, or a statement that details the potential conflict.

Covering letter

All manuscripts must be accompanied by a 1-page cover letter which specifies the type of article and summarizes the contribution it makes to the scientific literature. It should confirm that the manuscript is not under consideration by another journal and has not been previously published. It should contain an author contribution statement as well as a statement on any potential conflict of interests. The cover letter can be uploaded with the supplementary files.

Types of contributions

Original articles

These articles present new research results and should be limited to 4000 words and no more than 30 references. Section headings should include Abstract, Introduction, Methods, Results, Discussion, Conflicts of interest, Acknowledgements and References. Review articles are usually invited. Authors who wish to submit a review article should first liaise with the editor before manuscript submission. These articles should usually be limited to 5000 words and include no more than 50 references.

Reports of clinical trials

Reports of clinical trials should comply with the CONSORT guidelines and include a participant flow diagram. See http://www.consort-statement.org/ for details and for a template of the flow diagram.

The study should be included in a registry of clinical trials before commencement and the Methods section of the manuscript should cite the registration number. The Pan African Clinical Trials Registry (http://www.pactr.org/) is an example of such a registry.

Case reports

Concise reports of unusual or informative cases should be no more than 800 words (excluding the abstract and references). The abstract should not exceed 100 words. One table, up to two images, and up to 15 references may be included. All case reports must include a statement on ethics approval or a statement that permission for publication was granted by the patient or family.

Images in Nephrology

One or two high resolution images of exceptional interest may be submitted. These may be made available by the Journal to readers as PowerPoint slides. The accompanying text should be no more than 300 words, have a very brief abstract, and have a maximum of 6 references.

Congress proceedings

Abstracts of presentations at national or regional congresses can be submitted for publication in the Journal. Congress organisers are responsible for ensuring that the abstracts are correctly formatted and checked for errors. They will be published as received and are not sent for peer review. Congress proceedings are published as a single, searchable PDF document. The first page(s) should include the name, place and dates of the congress, and a concise list of abstract titles and authors.

Letters to the Editor

Letters should be no more than 250 words and relate to papers recently published in the Journal. They will be sent to the authors of the original paper for reply.

Manuscript layout

Submissions should be submitted as Microsoft Word files. UK English spelling should be used. The text should be Arial, font size 12. Pages should be A4 size and should be numbered consecutively, commencing with the title page.

Abbreviations must be spelled out the first time they are used, followed by the abbreviated form in parentheses.

Units of measurement. Système International (SI) units must be used e.g., kg, g, µg, cm, mm, etc. An exception is blood pressure which is reported in mmHg.

Trade names. Non-proprietary (generic) names should be used. The source of any new or experimental preparation should be given.

Manuscript sections

Title page:

Include the article title (use an initial capital letter only i.e., sentence case) and avoid abbreviations within the title, list all authors and their institutional affiliations at the time of the study, provide a short running title of up to 50 characters, the word count (not including the abstract, tables and references) and the name, address, and email address of the corresponding author.

Abstract and keywords:

Abstracts should be structured into Background, Methods, Results and Conclusions, and should not exceed 250 words in original or review articles, and 100 words in case reports. A French translation of the abstract may be submitted as an addition. Abstracts should not contain any figures, tables, or references. List a maximum of 6 keywords below the abstract.

Main text:

Original articles should include Introduction, Methods, Results and Discussion sections, each beginning on a new page. Statistical methods must be included in the Methods section. Methods not in common use should be described fully or supported by references. A statement on ethical approval should be included at the end of the Methods section.

Tables

Tables should not be submitted separately but should be included in the manuscript file directly after the paragraph in which it is first cited. All tables should be editable and not pasted into the manuscript as an image. They should be numbered consecutively, and each must have a brief caption placed above the table. Place footnotes below the table.

Figures

Figures should be submitted as separate, high-resolution images. Low-resolution copies may be embedded in the manuscript file. Multipanel figures must be provided as a single file. Figures should be numbered in the order they are mentioned in the text. Figure titles and legends should be included in the main manuscript, not in the graphic files. Photomicrographs should have a scale bar and the legend should include details of the staining technique. Patients shown in photographs should have their identity concealed or should have given their written consent to publication.

References

References should be relevant and not exceed 50 for review articles, 30 for original articles, 15 for case reports, 6 for images in nephrology and 5 for letters to the editor.

We strongly recommend the use of bibliographic software tools, such as EndNote or Mendeley, for reference management and formatting. For EndNote users, an Afr J Nephrol style file is available. The PLOS output style can also be used.

Citations in the text are indicated by the reference number(s) in square brackets, without using any spaces, e.g. [1,5-7].

At the end of the article, the references should be numbered in the order in which they first appear in the text. They should give the names of all authors unless there are more than six, when only the first six should be given, followed by "et al". This should be followed by the title of the article, the abbreviated journal name, the year of publication, the volume number and the full first and last page numbers. Consult PubMed for journal name abbreviations –

https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/.

References to books should give the title, followed by the place of publication, the publisher, the year, and the page numbers.

Examples:

Journal articles: Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005; 67:2089-2100.

Books:

Halperin ML, Goldstein MB, Kamel KS. Fluid, electrolyte, and acid-base physiology: a problembased approach. Philadelphia, PA: Saunders; 2010.

Book sections or chapters:

Topham PS, Chen Y. Renal biopsy. In: Floege Jr, Johnson RJ, Feehally J, editors. Comprehensive clinical nephrology. 4th ed. Philadelphia, PA: Saunders; 2010. pp. 75-84.

Reports:

Ghana AIDS Commission. National and sub-national HIV and AIDS estimates and projections. Available from: www.ghanaids.gov.gh. Accessed 17 June 2021.

Proofs

Upon acceptance, PDF proofs of the copyedited manuscript will be prepared. The corresponding author will be notified by email and should respond within 72 hours. Only minor corrections are allowed at this stage.

Copyright and Permissions

Appendix 3:

Ethical Approvals:

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

22 February 2022

Dr T Abulghasm
School of Clinical Medicine
College of Health Sciences
tahatheni1979@gmail.com

Dear Dr Abulghasm

Protocol: Review the prevalence and outcomes of Autosomal dominant polycystic kidney disease at a tertiary level hospital in KwaZulu-Natal, South Africa
Degree: MMed
BREC Ref No: BE081/19
New Title: Review the clinical presentation and the outcome of ADPKD attending IALCH in Kwa-Zulu Natal, South Africa during the period from 2013 - 2017

We wish to advise you that your application for amendments listed below received on 09 February 2022 for the above protocol has been **noted and provisionally approved** by a sub-committee of the Biomedical Research Ethics Committee pending:

1. Email from Prof Assounga that he approved additional co-supervisor
2. CV and TRREE RSA Ethics certificate for new co-supervisor.

Amendments noted :

1. Add co-supervisor: Dr. Kim de Vasconcellos
2. Change of title to new title of the study above.

Yours sincerely

[redacted]

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

18 June 2019

Dr T Abulghasm
School of Clinical Medicine
College of Health Sciences
tahatheni1979@gmail.com

Dear Dr Abulghasm

Protocol: Review the prevalence and outcomes of Autosomal dominant polycystic kidney disease at a tertiary level hospital in KwaZulu-Natal, South Africa
Degree: MMed **BREC Ref No: BE081/19**

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received 06 February 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 05 June 2019 to BREC letter dated 15 April 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 18 June 2019. **Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **18 June 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **09 July 2019.**

Yours sincerely

[redacted]

Prof D Wassenaar
Acting Chair: Biomedical Research Ethics Committee

cc: Postgrad administrator: SCMpgrad@ukzn.ac.za Supervisor: Assounga.agh@gmail.com

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 April 2021

Dr T Abulghasm
School of Clinical Medicine
College of Health Sciences
tahatheni1979@gmail.com

Dear Dr Abulghasm

Protocol: Review the prevalence and outcomes of Autosomal dominant polycystic kidney disease at a tertiary level hospital in KwaZulu-Natal, South Africa
Degree: MMed
BREC Ref No: BE081/19

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**18 June 2021**
Expiration of Ethical Approval:	**17 June 2022**

I wish to advise you that your application for Recertification received on 12 April 2021 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 May 2021.

Yours sincerely

[redacted]

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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

DIRECTORATE:
Health Research & Knowledge Management

Ref: KZ_201905_018

Dear Dr T Abulghasm
(UKZN)

Subject: Approval of a Research Proposal:

1. The research proposal titled **'REVIEW THE PREVALENCE AND OUTCOMES OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE ATTENDING INKOSI ALBERT LUTHULI CENTRAL HOSPITAL, IN KWAZULU-NATAL, SOUTH AFRICA'** was reviewed by the KwaZulu-Natal Department of Health.

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

2. You are requested to take note of the following:

   a. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   b. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   c. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete.*

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

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]
Dr E Lutge
Chairperson, Health Research Committee
Date: 30/05/19

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

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

Office of The Medical Manager
IALCH

Reference: BE 081/19
Enquiries: Medical Management

23 April 2019

Dr T Abulghasm
School of Clinical Medicine
College of Health Sciences

Dear Dr Abulghasm

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Review the prevalence and outcomes of Autosomal dominant polycystic kidney disease at a tertiary level hospital in KwaZulu-Natal, South Africa.**

Kindly take note of the following information before you continue:

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

Yours faithfully

[redacted]

cc **Dr L P Mtshali**
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

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

Office of The Medical Manager
IALCH

23 April 2019

Dr T Abulghasm
School of Clinical Medicine
College of Health Sciences

Dear Dr Abulghasm

Re: Approved Research: Ref No: BE 081/19: Review the prevalence and outcomes of Autosomal dominant polycystic kidney disease at a tertiary level hospital in KwaZulu-Natal, South Africa.

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

Kindly note the following.

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

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

Yours faithfully

[redacted]

cc ....
Dr L P Mtshali
Medical Manager

Appendix 4: Data collection tools:

Appendix 5: Raw data

KZ Number	Age	Gender	Race	Residence	Comorbidities
KZ00007461	2	1	B	1	B + D + E (Renal cell carcinoma)
KZ00010129	2	1	A	1	B + E (Ca Bladder)
KZ00018259	1	2	B	1	B
KZ00026969	1	1	A	0	B + E (hypothyroidism)
KZ00038207	1	1	A	1	B + E (Polycythemia+Renal stone)
KZ00049324	2	2	A	1	B + C + D + (Mega cisternia magna)
KZ00002623	2	1	A	1	B + E (Basal cell carcinoma + Gout)
KZ00003313	1	2	D	1	B
KZ00005838	2	2	D	2	B + C + E (osteoporosis)
KZ00007482	2	2	A	1	B + E (POS, pituitary macroadenoma, hypothyroidism)
KZ00084099	1	2	A	1	B + D
KZ00086680	2	1	A	1	B
KZ00089364	2	2	A	1	B + C + E (CVA)
KZ00090646	2	2	C	1	B
KZ00093860	2	2	B	0	B
KZ00099353	1	2	A	1	B
KZ00103278	0	2	A	1	B + C + E (lymphoma)
KZ00103552	2	2	B	1	B + E (UTI)
KZ00106555	1	2	B	1	B
KZ00117059	1	2	A	1	B
KZ00128354	0	2	A	1	E (Lichen Ntidus)
KZ00130056	1	1	A	1	B
KZ00132264	2	1	A	1	B + D
KZ00140617	1	2	A	1	B + D
KZ00149911	0	2	A	1	B
KZ00166346	2	2	B	1	B
KZ00173526	2	2	B	1	A + B + E (hemorrhoids)
KZ00179852	1	1	A	1	B
KZ00181110	1	1	B	1	A + B + E (hypothyroidism)
KZ00191173	1	2	A	1	B + E (hypothyroidism)
KZ00194147	1	1	D	1	B + E (polycythemia)
KZ00199520	2	1	A	1	B
KZ00221855	1	2	A	1	B + C + D + E (Gout)
KZ00224415	2	2	A	1	B + E (cerebral aneurysm)
KZ00227662	2	2	B	1	C + D

KZ00230184	1	2	A	1	B + D + E (CAD + Psoriasis)
KZ00245568	2	2	A	1	B
KZ00250725	1	1	B	1	B + E (testicular mass)
KZ00253712	1	1	B	1	B + D
KZ00267036	1	1	B	1	B
KZ00272942	0	1	B	1	E (UGIB)
KZ00281084	1	1	B	1	B + E (HIV)
KZ00284508	0	1	A	1	B + E (SLE)
KZ00286109	2	2	A	1	B + C
KZ00289404	1	1	A	1	B
KZ00295653	1	2	B	1	B
KZ00295957	0	1	C	1	B + C
KZ00300611	0	1	A	1	B
KZ00300972	2	1	D	1	B + E (transplanted kidney)
KZ00303558	1	2	B	1	B
KZ00305188	2	2	A	1	B + D
KZ00314676	1	1	A	1	B
KZ00319539	2	2	A	1	B + C
KZ00327228	1	1	B	1	B + E (osteoporosis)
KZ00335068	0	1	B	1	B
KZ00338036	1	2	B	1	B
KZ00338497	1	2	B	1	B
KZ00342861	2	2	C	1	B + D
KZ00343294	0	2	B	1	B
KZ00343313	1	2	B	1	B
KZ00345824	1	1	B	1	B
KZ00347706	1	2	B	1	B
KZ00348259	1	2	D	1	B
KZ00351934	1	1	B	1	B + E (CVA)
KZ00355142	1	2	A	1	B
KZ00363922	2	1	A	1	B + D + E (transplanted kidney)
KZ00372076	1	1	B	1	B + E (Gout + old CVA)
KZ00372872	1	2	B	1	B
KZ00505289	2	1	A	1	B + D + E (Renal stones)
KZ00506264	1	2	B	1	E (HIV + PTB)
KZ00512550	0	2	B	1	B
KZ00517892	1	1	B	1	A + B
KZ00518130	1	2	D	1	B + C

KZ00519127	1	2	B	1	B
KZ00520964	2	1	A	1	B
KZ00522359	1	2	B	1	B
KZ00525363	1	2	D	1	B
KZ00531342	1	1	B	1	B
KZ00548874	1	2	B	1	B + E (osteoporosis)
KZ00542571	1	2	A	1	B + A + E (osteoporosis)
KZ00340866	2	1	D	1	B + E (osteoporosis)

Duration of follow up	Presenting Renal Symptoms (At time of diagnosis)	Extra-renal manifestation
A	A1	0
C	A1	1
C	A1	0
C	C	0
B	A1	1
C	B1 (backache)	0
B	B1 (paiful foot)	1
B	B1 (bipedal edema)	0
C	B1 (bipedal edema)	1
A	C	0
C	A1	1
B	C	0
C	C	1
C	B1 (backache)	1
C	A1	1
C	B1 (UTI)	1
B	B1 (UTI)	0
C	C	1
C	A1	0
C	A1	0
B	C	0
B	B1 (backache)	0
A	C	0
B	C	1
B	C	0
B	A1	0

B	B1 (body itchiness)	1
B	C	0
B	C	1
B	B1 (backache)	0
B	A1	0
B	A1	1
A	B1 (bipedal edema)	1
A	B1 (bipedal edema)	1
A	C	0
B	C	1
A	C	1
A	B1 (low back pain/headache)	1
B	B1 (bipedal edema)	1
A	C	0
A	A1	1
A	C	0
A	A1	0
A	B1 (bipedal edema)	0
A	A1	0
A	A1	1
A	B1 (low back pain)	0
A	C	1
A	C	1
A	A1	1
A	B1 (low back pain/polyarthralgia)	0
A	B1 (dehydration)	1
A	C	0
A	C	0
A	C	0
A	B1 (vomiting/weakness)	1
A	B1 (paiful lower limbs)	0
A	C	0
A	B1 (anasarca)	0
A	B1 (dizziness)	1
A	C	0
A	C	1
A	B1 (bipedal edema)	1
A	C	1

A	B1 (anasarca)	0
A	B1 (anasarca)	0
A	B1 (acute GE)	0
A	B1 (Painful lowe limbs)	0
A	B1 (anasarka)	0
A	B1 (Painful lowe limbs)	0
A	B1 (bipedal edema)	0
A	B1 (bipedal edema)	0
A	B1 (Backache)	1
A	B1 (Backache)	1
A	C	0
A	C	0
A	B1 (acute GE)	0
A	C	0
A	C	0
A	A1	0
A	C	1

HIV status	CD4 count	ARVs	Outcome - ESRD	Cysts decortication or Aspiration
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	A	B
0	0	0	A	B
0	0	0	A	B
0	0	0	C	C
0	0	0	A	C
0	0	0	C	C
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B

0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B (Died – MI)	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	A	B
0	0	0	A	B
0	0	0	B	B
0	0	0	B	B
0	0	0	A	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
0	0	0	B	B
1	2	1	B	B
0	0	0	B	B
0	0	0	A	B
0	0	0	B	B
1	1	1	B	B
0	0	0	A	B
0	0	0	A	B
0	0	0	B (Died)	B
0	0	0	A	B
0	0	0	B	B
0	0	0	A	B
0	0	0	A	B
1	1	1	A	B
0	0	0	A	B
0	0	0	B	B
0	0	0	B	B
0	0	0	A	B
1	1	1	A	B
0	0	0	A	B

1	1	1	B	B
0	0	0	A	B
0	0	0	A	C
0	0	0	B	C
0	0	0	A	C
0	0	0	A	C
0	0	0	B	C
0	0	0	B	C
0	0	0	A	C
0	0	0	A	C
0	0	0	B	C
1	1	1	C	C
0	0	0	A	B
1	1	1	B	B
0	0	0	B	B
0	0	0	A	B
0	0	0	B	B
0	0	0	A	B
0	0	0	A	B
0	0	0	A	B
0	0	0	A	B
1	1	1	A	B
0	0	0	A	B
0	0	0	A	B
0	0	0	A	B

Nephrectomy	Kidney replacement therapy [HD/PD]	Kidney transplant	BP: First visit	BP: Last visit
A	0	0	1	2
B	0	0	1	1
B	0	0	2	2
B	0	0	1	1
B	0	0	1	2
B	0	0	1	2
B	1	1	1	1
A	1	0	1	0
B	1	1	2	1

B	0	0	1	1
B	1	0	1	1
B	0	0	2	1
B	0	0	2	2
B	0	0	1	2
B	0	0	0	2
B	0	0	1	1
B	0	0	1	1
B	0	0	2	2
B	0	0	2	1
B	0	0	1	2
B	0	0	1	1
B	0	0	1	0
B	0	0	1	1
B	0	0	2	1
B	0	0	1	1
B	0	0	2	1
B	0	0	1	1
B	1	0	1	1
B	1	0	1	1
B	0	0	1	1
A	0	0	2	1
B	1	0	1	1
B	0	0	2	1
B	0	0	1	1
B	0	0	2	2
B	0	0	2	2
B	0	0	1	2
B	0	0	1	1
B	0	2	2	2
B	1	0	2	0
B	0	0	1	1
B	0	0	2	1
A	1	0	2	2
B	1	0	2	2
B	0	0	1	2
B	1	0	2	2
B	0	0	1	2

B	1	0	2	2
B	1	1	2	1
B	1	0	1	1
B	1	1	2	1
B	0	0	1	2
B	0	0	2	2
B	1	0	1	1
A	1	0	2	1
b	1	0	1	1
b	0	0	1	2
b	1	0	2	1
b	1	0	1	1
b	0	0	1	1
b	1	0	2	2
b	1	0	1	1
b	0	0	1	2
b	0	0	1	1
b	1	0	2	2
b	1	1	1	2
b	1	2	2	2
C	2	2	1	2
b	1	0	0	1
b	0	0	2	2
b	0	0	2	2
b	1	0	1	1
b	0	0	2	2
b	1	0	2	2
b	1	0	1	1
b	1	0	2	2
b	1	0	2	1
b	1	0	1	2
b	1	0	2	2
b	1	0	2	0
b	1	0	2	1

Urea: First visit	Urea:Last visit	Creatinine: first visit	Creatinine: Last visit	eGFR: First visit	eGFR: Last visit
2	2	B	B	B	B
1	2	B	B	C	B
1	1	A	B	B	B
1	2	A	A	C	A
1	2	A	B	C	B
1	1	A	A	A	A
1	2	A	A	A	B
2	2	B	A	C	C
1	2	A	A	C	B
1	1	A	B	C	C
2	2	B	B	B	B
2	2	B	B	B	B
1	1	A	A	A	C
1	2	A	B	C	B
2	2	B	B	B	B
1	2	A	B	C	B
1	1	A	A	A	A
1	2	A	B	B	B
1	2	A	A	C	A
1	2	A	B	A	B
1	1	A	A	A	A
1	2	B	B	A	B
2	2	B	B	B	B
1	2	A	B	A	B
1	1	A	A	C	A
2	2	B	B	B	B
2	2	A	A	A	B
2	2	B	B	B	B
2	2	B	B	B	B
1	2	A	A	B	B
1	1	A	A	A	A
2	1	B	B	B	B
1	1	A	B	A	B
2	2	B	B	B	B
2	2	B	B	B	B
1	2	A	B	A	B
2	2	B	B	B	B
1	1	A	A	A	A
1	2	A	B	A	B
2	2	B	B	B	B

2	2	A	A	A	A
1	1	A	A	A	A
1	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
1	2	B	B	B	B
1	1	A	A	A	A
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
1	1	A	A	B	A
1	2	A	A	A	A
1	2	A	A	A	A
2	2	B	B	B	B
1	2	A	B	A	B
2	2	B	B	B	B
2	2	A	B	A	B
2	2	B	B	B	B
2	2	B	B	B	B
1	2	A	A	A	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
1	1	A	A	A	A
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
1	1	A	A	A	A
1	1	A	A	A	A
2	2	B	B	B	B
2	2	A	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B

2	2	B	B	B	B
2	2	B	B	B	B
2	2	B	B	B	B

iGFR	Hemoglobin	CRP	Random blood glucose	HbA1C	UPCR-protein	UMCS - MICRO
1	A	0	2	1	2	2
1	B	2	2	1	1	0
1	A	0	1	0	1	0
0	A	0	1	0	1	2
1	A	0	2	2	1	0
1	A	0	2	1	1	2
1	B	1	1	1	1	0
0	B	2	2	0	1	0
1	B	2	1	0	1	0
0	B	0	2	2	2	2
1	B	2	2	0	1	0
0	C	1	2	1	1	0
1	C	1	2	2	1	0
1	B	1	1	2	2	2
1	A	1	1	0	1	0
1	A	2	1	1	1	2
1	A	1	2	1	1	2
0	A	0	1	0	2	0
1	A	1	1	0	1	2
1	B	1	1	2	1	0
0	A	0	1	0	1	2
1	B	1	3	2	1	2
0	A	1	1	1	2	2
1	A	1	2	2	1	2
1	A	0	1	0	2	0
1	A	1	2	2	2	0
1	A	0	1	0	2	0
0	A	0	2	0	2	2
1	B	0	2	0	1	2
1	A	1	2	1	1	2
1	A	0	1	1	2	2

1	A	2	2	1	2	2
1	B	1	2	2	1	0
0	B	0	1	1	2	2
1	A	0	1	1	1	0
0	A	2	3	2	1	0
1	B	0	1	1	2	2
0	A	0	2	0	2	2
1	A	0	2	2	1	0
1	B	2	1	0	2	0
0	A	1	0	0	2	2
0	A	2	2	0	2	0
1	A	2	1	0	2	0
0	B	2	1	1	2	2
1	C	2	1	1	2	0
1	C	2	1	1	2	1
0	A	0	1	0	2	0
1	A	0	1	0	1	0
1	A	0	1	0	1	2
0	B	2	2	0	1	0
0	A	1	3	1	1	0
0	A	1	1	0	2	0
1	A	0	1	0	2	2
0	B	2	0	0	2	2
0	A	2	1	0	2	2
0	C	1	0	1	2	1
1	B	2	1	0	1	0
0	B	1	2	0	1	0
1	C	1	1	0	1	2
0	A	1	1	0	2	0
0	B	2	2	0	2	0
0	A	2	2	0	1	2
1	A	2	1	0	1	0
0	A	0	1	0	2	2
0	B	1	1	0	1	0
0	A	0	2	0	2	2
0	A	0	1	1	2	0
0	A	1	1	0	1	0
1	B	2	2	2	1	1

1	A	2	1	2	1	0
1	A	1	1	0	1	0
0	C	2	2	0	2	0
1	A	1	1	1	1	0
0	C	2	1	0	1	2
1	B	1	1	1	1	0
0	B	1	1	0	1	2
0	C	1	2	0	1	0
0	B	2	1	0	1	2
1	B	2	0	0	1	2
1	A	1	0	0	1	0
0	A	0	0	0	2	1

U/S Right kidney	U/S Left kidney	U/S liver	CT abdomen: compatible with PCKD	MRI abdomen/brain
0	1	1	0	0
0	2	2	1	0
2	2	1	1	0
0	2	1	0	0
2	2	2	1	0
1	1	1	0	0
0	1	2	0	0
2	2	0	0	0
3	1	2	1	0
3	3	0	0	2
2	2	2	0	0
2	2	0	0	0
0	2	2	0	0
2	2	2	0	0
2	2	2	0	0
2	2	2	0	0
2	2	1	0	0
2	2	2	1	0
2	2	0	1	0
2	2	0	0	0
2	2	1	0	0
2	2	1	0	0
2	2	1	0	0

2	2	2	0	0
2	2	1	0	0
2	2	1	1	0
2	2	2	0	0
2	2	1	0	0
2	2	2	1	0
2	2	1	1	0
2	2	0	0	0
2	2	2	1	0
2	2	2	1	0
2	2	0	0	0
2	2	1	1	1
2	2	2	0	0
2	2	2	0	0
2	2	2	1	0
2	2	2	0	0
1	0	1	0	0
2	2	2	1	0
2	2	1	0	0
0	2	1	1	0
0	1	1	0	0
2	2	1	0	0
2	2	2	0	0
2	2	1	0	0
2	2	2	1	0
2	2	2	0	0
2	2	2	1	1
2	2	1	0	0
2	2	2	0	0
2	2	1	0	0
2	2	1	0	0
2	2	1	1	0
2	2	2	1	0
2	2	1	0	0
2	2	1	0	0
2	2	0	0	0
2	2	2	1	0
2	2	1	0	0

2	2	2	1	0
2	2	2	0	0
2	2	2	0	0
2	2	1	0	0
2	2	0	0	0
2	2	1	0	0
2	2	0	0	0
2	2	1	0	0
2	2	1	0	0
2	2	0	0	0
2	2	1	0	0
2	2	2	0	0
2	2	2	1	0
2	2	1	0	0
2	2	1	0	0
2	2	1	0	0
2	2	1	0	0
2	2	1	0	0
2	2	1	0	0
2	2	2	1	0

Histopathology: Kidney biopsy	Genetic analysis: PKD-1 gene/ PKD-2 gene or Allelic heterogeneity	Urine dipstick protein	Urine dipstick RBCs	Urine dipstick pH
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	B	A	A
0	0	A	A	A
0	0	B	B	A
0	0	B	B	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	B	A	A
0	0	A	A	A
0	0	B	B	A

0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	B	B	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	C	C	C
0	0	B	B	A
0	0	A	A	A
0	0	A	A	A
0	0	A	B	A
0	0	A	A	A
0	0	B	A	A
0	0	B	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	B	A
0	0	A	B	A
0	0	A	C	A
0	0	A	A	A
0	0	B	A	A
0	0	C	C	C
0	0	B	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	B	A	A
0	0	B	B	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A
0	0	A	A	A

0	0	C	C	C
0	0	A	A	A
0	0	C	C	C
0	0	A	B	A
0	0	B	B	C
0	0	C	C	C
0	0	A	A	A
0	0	BA	A	A
0	0	C	C	C
0	0	A	A	A
0	0	A	A	A
0	0	B	A	A
0	0	A	A	A
0	0	B	A	A
0	0	B	B	B
0	0	C	C	C
0	0	A	A	C
0	0	C	C	C
0	0	B	A	A
0	0	A	A	A
0	0	B	A	A
0	0	A	A	A
0	0	C	C	C
0	0	B	B	C
0	0	C	C	C
0	0	C	B	C
0	0	C	B	C
0	0	B	B	C