THE USE OF CHRONIC DIALYSIS IN A RESOURCE-POOR ENVIRONMENT: DEMOGRAPHIC FEATURES AND TRANSPLANT READINESS AT HELEN JOSEPH HOSPITAL RENAL UNIT

Dr Dinen Parbhoo

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters in Medicine (MMed)

Johannesburg 2019

DECLARATION

I, Dr Dinen Parbhoo declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Internal Medicine at the University of Witwatersrand, Johannesburg. It has not previously been submitted for any degree or examination at any other University.

Dr Dinen Parbhoo MBBCh (Wits), Dip HIV Man (SA), FCP (SA)

DEDICATION

To

My parents and my wife, who believed in me every step of the way.

ABSTRACT

Background

Chronic kidney disease (CKD) places a considerable economic strain on health care systems. In South Africa resource limitations in the public sector mandate that patients with end stage renal disease (ESRD) are only offered dialysis if they qualify for renal transplant. Thus, chronic dialysis serves as a bridge to transplantation.

Objectives

The primary objective of this study was to describe the patients on the chronic dialysis program with regards to demographic features, aetiology of renal failure, associated chronic co-morbidities and transplant readiness. Secondary objectives included the determination of the type and duration of dialysis used and the documentation of any possible differences between the haemodialysis (HD) and peritoneal dialysis (PD) groups and the HIV positive and negative patients.

Methods

A cross-sectional record review was conducted of all patients receiving chronic dialysis at the Helen Joseph Hospital's Renal Unit as at September 2016. Information regarding demographic features, disease profile, year of initiation of dialysis, year of presentation, Human Immunodeficiency Virus (HIV) status and transplant readiness was collected. All data was analysed at a 95% confidence interval and a p value of <0.05 was considered significant.

Results

There were 92 patients on chronic dialysis, 46 each on PD and HD. The mean (SD) age of patients in this study was 43.8 years (10.8). There was a slight female predominance (51.1%). The predominant ethnic group was African (64.1%). The leading causes of ESRD were hypertension (35.9%) followed by diabetes mellitus (10.9%). The most frequent comorbidity was hypertension (98.9%) followed by HIV infection (36.1%). The median time that patients spent on dialysis before presentation for transplant listing was 2 years (range 0-9 years). At the time of analysis, 27 patients (29.4%) were eligible for transplant and 38 patients (41.3%) were in the process of transplant eligibility evaluation. Twenty-seven patients (29.4%) were ineligible for transplant. Of those eligible for transplant, 21 were listed for transplant and 6 were awaiting presentation for listing. There were no differences between the HD and PD groups or the HIV positive and negative groups with regards to qualification for transplant.

Conclusion

The demographic features and underlying aetiologies of our cohort are similar to national figures with only the racial composition being different. The proportion of patients listed for transplantation (22.8%) and median time for work-up (2 years) are both sub-optimal. Improved efficiency in the evaluation of transplant eligibility is required in order to optimize the appropriate allocation of dialysis in a resource-limited setting.

ACKNOWLEDGEMENTS

I would like to thank my family, friends and teachers for their unwavering support. I would also like to thank the Helen Joseph Hospital Renal unit.

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List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
CKD	Chronic kidney disease
ECG	Electrocardiogram
echo	Echocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
HD	Haemodialysis
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
KDIGO	Kidney Disease: Improving Global Outcomes
OR	Odds ratio
PD	Peritoneal dialysis
pmp	Per million population
PRA	Panel reactive antibody
RRT	Renal replacement therapy
SA	South Africa
SD	Standard deviation
UK	United Kingdom
USA	United States of America
USRDS	United States Renal data system
ZAR	South African Rand

CHAPTER 1: Protocol and literature review

1.1 Introduction

Chronic kidney disease (CKD) has become a global health problem resulting in an economic burden in all affected countries (1-4). The prevalence of CKD is estimated at 13.9% in Sub-Saharan Africa, in keeping with the global estimate of 13.4% (5).

In 2010, CKD was the 18th leading cause of death worldwide (6); by 2015, it had risen to be the 12th most common cause of death (7). According to the Global Burden of Disease Study published in 2016, deaths due to CKD had risen by 31.7% from 937 700 people in 2005 to 1.2 million people in 2015 (7). Chronic kidney disease is now the 17th leading cause of global years of life lost with an 18.4% increase since 2005 (8).

Global life expectancy has increased from 61.7 years in 1980 to 71.8 years in 2015 which is likely to have contributed to the increasing prevalence of CKD (5, 7). In Sub-Saharan Africa life expectancy has improved between 2005 and 2015 due to decreased Human Immunodeficiency Virus (HIV) related deaths (7). This is due to increased access to antiretroviral therapy (ART) (9).

In developing countries rapid urbanization, poor diet and inactivity have contributed to the increasing prevalence of obesity, hypertension and diabetes (8). This has resulted in an increase in CKD (8). The overall rate of death from CKD secondary to diabetes mellitus has increased by 39.5 %, from 299 400 deaths in 2005 to 417 800 deaths in 2015, with the largest increases documented in Mexico, India and China (7, 8).

In low to middle income countries, inadequate risk factor management in patients with CKD contributes to the increased burden of end stage renal disease (ESRD) (8). Primary health care providers fail to identify CKD, non-nephrologists are unaware of CKD guidelines and there is an overall failure to implement CKD guidelines (8). These countries are also subject to an unbalanced nephrologist to patient ratio (7).

In Sub-Saharan Africa the large burden of communicable diseases contributes to the burden of non-communicable diseases such as CKD. The prevalence of infectious causes of CKD such as HIV, schistosomiasis, and infectious glomerulonephritis are important contributors to the

prevalence of CKD in this region (9). Sub-Saharan Africa has more than 22 million people living with HIV (9). As people with HIV live longer on appropriate treatment, they too are at increased risk for developing ESRD due to causes other than HIV itself, further contributing to the prevalence of CKD in this region (9-12).

HIV causes a variety of renal disease including acute kidney injury, CKD, HIV associated renal disease and HIV- treatment related renal toxicity (13). Acute kidney injury is more prevalent in the HIV infected versus the general population and is associated with an increased risk of adverse outcomes (13). HIV associated kidney disease includes HIV-associated nephropathy (HIVAN), HIV immune complex kidney disease (HIVICK) and, less commonly, thrombotic microangiopathy (13, 14).

In African patients with HIV infection, comorbidities such as hypertension, diabetes and hepatitis C, lead to an accelerated progression of CKD (13). Many antiretroviral drugs cause renal dysfunction and drug interactions may cause further deterioration of renal function (13).

Due to a lack of medium to high quality evidence and heterogeneity used in the definition of CKD in the available published data, the prevalence of CKD in many areas of Sub-Saharan Africa is not known (15).

1.2 Chronic kidney disease

1.2.1 Definition

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD is defined as renal damage (structural or functional) which is present for more than three months duration (16). The time frame distinguishes acute from chronic kidney disease (16).

1.2.2 Classification

Chronic kidney disease is classified according to cause, estimated glomerular filtration rate (eGFR) category (Table 1) and albuminuria category (Table 2) (16). Other markers include: abnormalities in urine sediment and serum electrolytes (due to tubular disorders); histological diagnosis, structural defects on imaging and history of kidney transplantation (16).

Table 1: Glomerular filtration rate (GFR) categories in chronic kidney disease

GFR Category	GFR (ml/min/1.73m^2)	Terms
G1*	>90	Normal/ high
G2*	60-89	Mildly decreased
G3a	45-59	Mild to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

KDIGO Guidelines, 2012

*In the absence of evidence of kidney damage neither GFR category G1 nor G2 fulfil the criteria for CKD (17).

Table 2: Albuminuria categories in chronic kidney disease

Category*	Albumin Excretion Rate (mg/24hrs)	Albumin to creatinine ratio (mg/mmol)	Terms
A1	<30	<3	Normal to mildly increased
A2**	30-300	3-30	Moderately increased
A3**	>300	>30	Severely increased

KDIGO Guidelines, 2012

*Classifying CKD according to the cause, eGFR and albuminuria category allow for one to predict prognosis and risk stratify patients (17).

**Category A2 and A3 independently fulfil the criteria for CKD.

1.2.3 Aetiology

In Sub-Saharan Africa, ESRD presents in younger adults between 20-50 years of age. In South Africa the primary underlying causes were hypertension (45.6%) and glomerular disease (52.1%) (18). This data was published in 1994 (18). In developed countries it is seen largely in the middle aged to elderly population due to the prevalence of hypertension and diabetes in these patients (19).

In South Africa (SA), 30.4% of the adult population have hypertension (20, 21). There is an increasing prevalence of hypertension in urban versus rural black South Africans. This increase has been attributed to the consumption of excess salt, greater stress and less physical activity (22). Hypertension has been associated with the risk for CKD through the development of damage to the renal vasculature with resultant intimal thickening and luminal narrowing ultimately leading to glomerulosclerosis (23, 24).

Intrinsic glomerular disease due to a variety of causes, is more prevalent in Africa and exists in a more severe form than in developed countries, with a poorer response to treatment and rapid progression to renal failure (25).

In 2012, the prevalence of diabetes mellitus in SA was estimated at 9.5% of the population above 15 years of age (26). Diabetic nephropathy involves glomerular sclerosis, tubular and interstitial damage, with the typical nodular mesangial expansion (Kimmelstiel-Wilson nodules) seen in 40-50% of patients with diabetic nephropathy (27). Diabetic nephropathy has a 14-16% prevalence in SA (18, 25).

Obstructive uropathy and ureteric reflux may lead to CKD if not identified and treated timeously (28). This occurs due to interstitial inflammation, tubular apoptosis and interstitial fibrosis (28).

Other causes of CKD include severe acute kidney injury from any cause, toxin induced renal damage, and cystic kidney disease (3). In many cases, due to the late presentation of patients, the exact aetiology of ESRD cannot be elucidated (3).

1.2.4 Treatment modalities

A multidisciplinary care setting is recommended for patients with any chronic condition (29). Treatment modalities for ESRD include dietary counselling, psychological and social care, and a nephrology unit for renal replacement therapy (RRT) (16). Conservative management is reserved for those who refuse RRT, where dialysis would not improve quality or duration of life and those who do not qualify for RRT due to financial constraints at public hospitals (1, 30, 31). Renal replacement therapy is the active form of management and includes haemodialysis (HD), peritoneal dialysis (PD) and renal transplantation.

1.3 Renal replacement therapy

Dialysis is a procedure whereby wastes and toxins are removed from the blood, fluid and electrolyte imbalances are adjusted by utilizing countercurrent flow rates at which substances diffuse through a semipermeable membrane (32). Dialysis should be initiated once ESRD occurs as an interim measure prior to renal transplantation.

According to the KDIGO guidelines, in patients with CKD, dialysis should be initiated when one or more of the following are present (16):

- Symptoms and signs of kidney failure
- Fluid overload secondary to kidney failure
- Uncontrolled blood pressures
- Deterioration in nutritional status despite adequate diet
- Cognitive impairment (uraemic encephalopathy)

These symptoms often occur in the eGFR range between 5-10 ml/min/1.73m^2 (16).

1.3.1 Types of renal replacement therapy

Haemodialysis involves removing blood from the patient's circulation, passing it via an extracorporeal circuit through a dialysis machine which contains a synthetic dialysis membrane and returning the purified blood back to the patient (33). In PD, the peritoneum acts as the semi permeable membrane; dialysate fluid is introduced into the peritoneal cavity, and removed after diffusion of toxins between the patient's peritoneal membrane capillaries and the dialysate fluid has occurred (33).

Transplantation is the ideal form of RRT as it improves the quality of life (physical, mental, emotional and social functioning) and reduces the mortality risk for most patients (17, 34-36). In a systematic review, 76% of studies found a lower risk of death in transplant patients compared to those on dialysis (36). Transplantation also reduced the risk of cardiovascular events such as myocardial infarction, stroke, ischaemic heart disease and heart failure (36). There was a reduced rate of infection amongst transplant patients despite immunosuppressive therapy (36). Even though there is an increased short term (0-3 months) risk of death after transplantation due to the surgery itself and immunosuppressive therapy, the long term survival is increased when compared to patients on chronic dialysis (37). According to The American Society of Transplant Physicians, renal transplantation should ideally be performed at the exact time that the patient requires dialysis, unfortunately this is rarely possible (38).

1.3.2 Costs of different modalities of renal replacement therapy

Although no accurate local data is available on the costs of RRT in SA, it is estimated to be in excess of $13 963 (ZAR 200 00.00) per person per year (39). In the United States of America (USA) expenditure per person year of HD is $87 945; PD $71 630 and transplant $32 922 (40). In the United Kingdom (UK) the cost of HD ranges between $26 919 – $45 405 and PD between $20 185 – $28 074 per person per year (41). Some developing countries have much lower estimated costs per person per year, India reported lower annual costs ($3 000) for HD, achieved by means of various cost saving strategies (42, 43). The cost of post transplantation care is significantly less than dialysis and therefore in an ideal setting most patients requiring RRT should be transplanted.

1.3.3 Access to renal replacement therapy

Of all the patients receiving RRT internationally in 2010, it was estimated that 92.8% resided in high or high-middle income countries and the rest in low or low-middle income countries (4). Liyanage *et al*. estimated that in five countries (China, India, Indonesia, Pakistan and Nigeria), home to half the world's population, less than 25% of eligible patients could access RRT (4).It is further estimated that 13.9% of the adult population in Sub-Saharan Africa have CKD; however, less than 5% of patients with ESRD receive RRT (39). In certain areas of middle and east Africa, it is also estimated that less than 3% of people requiring RRT have

access to it (4). The low number of people on RRT in these developing countries is not due to low levels of renal diseases, but rather a lack of access to RRT (4, 39).

1.3.4 Transplantation rates worldwide

Data from the United States Department of Health and Human Services in November 2016 indicated that there were 100 791 people (all ages) awaiting renal transplantation (44). The median waiting period to first transplantation was 3.6 years (44). In 2014, 17 107 renal transplants were performed in the USA (44).

Amongst the 24 renal transplant centres in the UK, 3 347 kidney transplants were performed between 01 April 2016 and 31 March 2017 (45). There were 8 453 patients listed for transplantation of which 3 256 (38.5%) were suspended at the time (45). The median waiting period to first transplantation was 2.3 years. The median time from starting dialysis to renal transplantation was 3.15 years (45).

Data from the 129 transplant centres in Brazil in December 2016 showed 21 264 patients were awaiting kidney transplantation and 5 492 renal transplants were performed that year (46).

In a recent systematic review of renal registries worldwide there is a paucity of data largely from emerging economies due to lack of national renal registries (47).

1.4 The South African context

In 2015 the population of SA was estimated to be 55 million (48). The World Bank regards SA as an upper-middle income country; however, significant disparities exist in per capita income due to historical inequalities. Approximately 62% to 72% of the population relies solely on public health care and only 28-38% have access to private health care (5, 48). There are also large disparities in terms of access to renal dialysis units based on geographical location in SA. The 2013 and 2015 Annual Report from the South African Renal Registry notes that the provinces of Limpopo and Mpumalanga do not have any state-funded treatment centres (48, 49). Transplant centres are only available in 4 of the 9 provinces (48, 49).

1.4.1 Eligibility for dialysis

Due to resource and financial constraints in the public sector of SA, not all patients requiring RRT will receive it (5, 50). Current SA guidelines for RRT in the public sector mandate that eligibility for transplantation determines acceptance for dialysis (5, 51). Transplant criteria are designed to stratify patients to ensure optimal outcomes following transplantation (5). The transplantation criteria are used to (52):

- Identify co-morbidities that significantly shorten patient survival (e.g. significant coronary vascular disease, cerebrovascular disease, peripheral vascular disease, uncontrolled diabetes mellitus, liver cirrhosis and malignancy) where renal transplantation would not improve patient survival.
- Identify factors that could affect post-transplant survival (e.g. HIV and opportunistic infections, obesity, diabetes mellitus, living donor versus deceased donor).
- Determine if the transplantation is technically feasible (e.g. significant peripheral vascular disease where graft dysfunction may occur).
- Guide post-transplant immunosuppression (e.g. cardiovascular disease, epileptics, and those with coagulation disorders- due to drug interactions).

The National Department of Health in conjunction with the South African Renal Society have developed exclusion-based criteria for transplant eligibility based on medical, psychological and compliance parameters (Appendix A) (51). Age and HIV status are not regarded as absolute contraindications to the provision of chronic dialysis (34, 51). In these cases, other patient and resource-related factors are considered in the decision-making process (34, 51, 53).

In this regard, further guidelines have been published in SA, specifically additional criteria for HIV infected individuals, and include (Appendix B) (54):

- Stability on antiretroviral therapy with good adherence to treatment for six months
- Absence of AIDS defining illnesses
- A CD4 count >200/ul for more than six months
- Suppressed viral load for more than six months (<50 copies/ml)

1.4.2 The transplant workup

In the state sector, patients are subjected to a pre-dialysis initiation transplant work-up, which includes:

- History
- Physical examination (including Body mass index (BMI))
- Review of social circumstances
- Cardiac evaluation (electrocardiogram (ECG), echocardiogram (echo), exercise stress test, coronary angiogram and carotid doppler, as indicated)
- Chest X-ray
- Gastroscopy
- Voiding cysto-urethrogram
- Abdominal and pelvic ultrasound
- Serological testing for chronic infection (HIV, Hepatitis B and C)
- Pap-smear for female patients.

South African Guidelines state that a BMI greater than 35 kg/m^2 is an exclusion factor for transplant, due to an increased rate of complications post-transplant and shorter graft survival (34).

1.4.3 Modality of renal replacement therapy

Once the decision has been made to accept a patient for RRT, the modality of replacement has to be decided.

To assess patient eligibility for PD, many factors need to be evaluated (34). Social factors- including home size and cleanliness, access to toilet and sink, storage space for supplies and physical access to the home so that delivery of dialysate can occur (34). Medical factors such as functional status, previous abdominal surgeries, psychiatric conditions, memory loss, vision or hearing impairment, also need to be considered (34). Peritoneal dialysis has the advantage of being patient-centred. It allows most individuals to maintain "normal" work schedules with minimal time lost from work due to hospital consultations and inpatient dialysis treatment. According to the 2012 and 2013 USRDS reports, PD showed better survival than HD in patients in the first five years after initiating RRT (55, 56).

For patients who do not qualify for PD, HD may be offered. In state hospitals in SA, HD slots are determined by the number of functional dialysis machines in the renal unit and the availability of trained dialysis staff (50). This limits the number of patients that can receive chronic HD at each unit (50).

1.4.4 South African Dialysis and Transplant Registry data

1.4.4.1 Demographic features

In 2015, the SA population totalled 55 million people, of whom 51.1% were female. The ethnic breakdown was: 80.5% Black/ African, 8.8% were of mixed ethnicity (Coloured), 8.3% were White and 2.5% were Indians/Asians (57). Twenty-four percent (13.2 million) of the country's population resides in Gauteng, which has 7 of the country's 30 public sector renal centres. These host 958 of the 3 318 public sector patients receiving RRT in SA (48, 57).

1.4.4.2 Aetiology of ESRD in South Africa

According to the South African Renal Registry reports of 1994, 2013 and 2015 on the causes of ESRD of patients on RRT have differed slightly, but hypertension and diabetes are still the most prevalent (Table 3).

Table 3: Aetiologies of end stage renal disease in South Africa from 1994, 2013 and 2015 (48, 49, 58)

1994	**2013**	**2015**
Glomerulonephritis (52.1%)	Glomerulonephritis (36.5%)	Uncertain/ not stated (34.1%)
Hypertension (45.6%)	Hypertension (31.7%)	Hypertension (33.7%)
	Diabetic nephropathy (11.8%)	Diabetic nephropathy (14.4%)
	Uncertain/ not stated (8.6%)	Glomerular disease (9.5%)
	Other (8.3%)	Other (3.9%)
	Cystic kidney disease (3.1%)	Cystic kidney disease (2.9%)
		Obstruction and reflux (1.5%)

The differences noted may be attributable to issues with record keeping and differing access to care (48). Over the same period of time there has been a change in the socioeconomic climate of the country with a resultant impact on disease profiles (12). Compared to aetiologies reported worldwide (Table 4) SA has a higher prevalence of hypertension. In SA patients tend to present later with ESRD and renal biopsies are not routinely performed in all patients with ESRD (48). This may impact on ascertaining the aetiology, hence the uncertain aetiology in 34.1% of patients with ESRD in 2015 (48). The large number of patients with an uncertain diagnosis in 2015 may also be due to a change in the coding system used to record chronic kidney disease (48).

Table 4: Aetiology of end stage renal disease worldwide (59-62)

USA (2016)	UK (2016)	India (2010)	Libya (2010)
Diabetic nephropathy (38.12%)	Diabetic nephropathy (27%)	Diabetic nephropathy (31%)	Diabetic nephropathy (28.4%)
Hypertension (25.68%)	Other (18%)	Other (26%)	Glomerulonephritis (20%)
Other (19.91%)	Uncertain (15%)	Uncertain (16%)	Other (17.5%)
Glomerulonephritis (16.29%)	Glomerulonephritis (14%)	Glomerulonephritis (14%)	Hypertension (15.8%)
	Hypertension (7%)	Hypertension (13%)	Uncertain (10.2%)
	Polycystic Kidney disease (7%)		Congenital and hereditary (8.1%)

1.4.4.3 Distribution of patients on RRT

The South African Renal Registry's annual reports between 1994 and 2015 indicate a marked increase in the absolute number of patients on RRT, this is largely due to improved capacity in the private sector, which only supplies 28-38% of the country's population (48, 49, 58). In addition, the transplantation rate has fallen from 8.7 per million population (pmp) in 1994 to 4.6 pmp in 2015 with the absolute number of renal transplants performed in 1994 being 299 compared to 254 in 2015 (48, 58). This may be due to the high cost of performing the transplantation and a shortage of organ donors (Table 5).

Table 5: Renal replacement therapy in South Africa (48, 49, 58)

	1994	**2013**	**2015**
Population (million)		52.98	54.96
Total on RRT	3399	8840	10 360
Treatment rate (pmp)	99	167	189
HD (total)	1077	6295	7529
Public		1507	1517
Private		4788	6012
PD (total)	461	1238	1440
Public		809	963
Private		429	477
Functioning transplants	1578	1307	1391
New transplants done (pmp)	299 (8.7)	246 (4.6)	254 (4.6)
New transplants in public sector		85	95
New transplants in Gauteng public sector only		23	35

pmp: per million population

There are currently 4300 listed patients awaiting different organ transplants in SA (63). In 2016, 37% of kidney recipients were related to the donor thus leaving 63% dependent on other living or cadaveric donors (63). Renal replacement in SA has not increased proportionally to the population growth and the current infrastructure is unable to cope with the growing burden of ESRD (48, 64).

1.4.5 Available local data at Chris Hani Baragwanath Academic Hospital

Chris Hani Baragwanath Academic Hospital (CHBAH), situated in Soweto, Johannesburg, is the largest hospital in Southern Africa with one of the largest state renal units (65). It serves a population of millions of patients excluding those in surrounding provinces. The renal unit provides an acute haemodialysis service for any patient requiring it at the hospital. However, patients are accepted onto the chronic dialysis program only if they fulfill the stringent transplantability criteria (65).

Transplant statistics in August 2018 at CHBAH renal unit are shown in the table below (personal communication, 17 September 2018: Appendix C):

Table 6: Dialysis data from Chris Hani Baragwanath Academic Hospital

	Haemodialysis Number (%)	**Peritoneal dialysis Number (%)**	**Total number Number (%)**
Chronic dialysis	95	65	160
On transplant list	33	37	70
Transplanted in August 2018	1	1	2
Awaiting listing	51	22	73
Ineligible for transplantation	11 (11.6)	6 (9.2)	17 (10.6)

Those awaiting listing included patients with an incomplete work-up.

1.4.6 Areas which lack data in South Africa

There is currently no published data on the utilization of dialysis as a scarce resource with regards to:

- The proportion of patients fully worked up for transplantation currently receiving chronic dialysis in the public sector
- The proportion of patients on the chronic program who qualify for renal transplantation
- The proportion of patients on chronic dialysis who have been presented for transplantation
- How many of the patients who do not qualify are due to reversible or irreversible factors
- The proportion of patients still undergoing transplant evaluation
- The time taken to complete transplant evaluation

1.5 Conclusion

The purpose of this audit is to evaluate the characteristics and transplant readiness of the patient group receiving chronic dialysis at Helen Joseph Hospital. At present, specific information pertaining to the individual renal units is not published in SA. The information obtained in this study can be used to compare the provision of dialysis to other renal units (locally and abroad), and to review the utilization of this resource in our renal unit.

1.6 Problem statement

End stage renal disease is becoming a major burden on the SA health system. Due to advances in other spheres of health care and an increase in the average life expectancy, improvement in HIV treatment and access to care, the number of patients with ESRD has increased disproportionally to the availability of medical care for this disease (31, 50).

Cost-benefit analysis indicates that time spent on dialysis should be minimized with a view to early transplantation.

The demographic features of patients currently on the chronic program and transplant readiness need to be determined in order to ensure effective utilization of this scarce resource.

1.7 Aims and objectives

1.7.1 Aim

The aim of this study is to describe the demographic features and transplant readiness of patients currently on the chronic dialysis program at the Helen Joseph Hospital's renal unit.

1.7.2 Objectives

The objectives of this study were the following:

- To describe patient demographic features, aetiology of renal failure and chronic co-morbidities.
- To determine the type and duration of dialysis used and determine whether any differences exist between the HD and PD groups.
- To review the transplant readiness of the patients on dialysis.
- To determine the proportion of patients on the dialysis program who are eligible or ineligible for transplantation and whether there is any statistically significant difference between the HD and PD groups or HIV positive versus HIV negative groups.

1.8 Methods

1.8.1 Study design

A cross sectional study design was undertaken for the month of September 2016. Data was collected to facilitate the analysis of the disease profile, patient demographic features, type of dialysis and work-up performed for transplant readiness.

1.8.2 Setting

The study was conducted at the renal unit at Helen Joseph hospital. It is a regional academic hospital complex, together with Rahima Moosa Mother and Child hospital, situated in Newclare, Johannesburg. It serves a population of approximately one million people from mainly region B, C and D (Figure 1). The population is urban and low to middle income; thus most patients are dependent on state health care services.

Region A	Diepsloot, Kya Sands, Dainfern, Midrand, Lanseria, Fourways
Region B	Randburg, Rosebank, Emmarentia, Greenside, Melville, Mayfair, Northcliff, Rosebank, Parktown, Parktown North
Region C	Roodepoort, Constantia Kloof, Northgate, Florida, Bram Fischerville
Region D	Doornkop, Soweto, Dobsonville, Protea Glen
Region E	Alexandra, Wynberg, Sandton, Orange Grove, Houghton
Region F	Inner City, Johannesburg South
Region G	Orange Farm, Weilers Farm, Ennerdale, Lenasia, Eldorado Park, Protea South

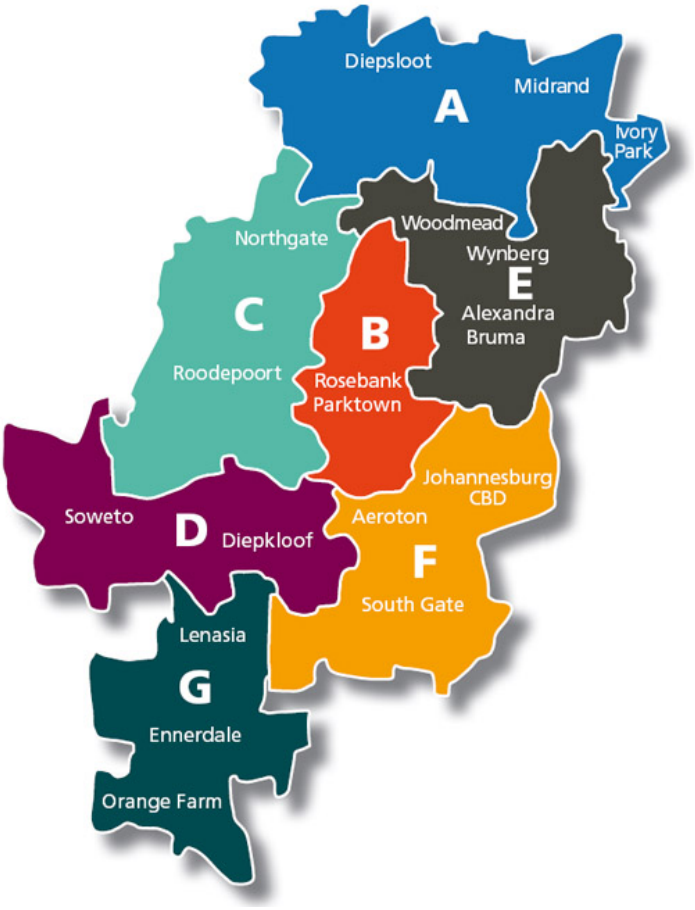

Figure 1 Map of the seven regions in Johannesburg (66)

1.8.3 Sample method

All files of patients on the chronic dialysis program at Helen Joseph Hospital were reviewed.

1.8.4 Sample size

All patients on chronic dialysis in September 2016 were included in the study. A total of 92 patients, comprising 46 on HD and 46 on PD, were included.

1.8.5 Inclusion criteria

All patients accepted to the chronic dialysis program at the Helen Joseph Hospital renal unit were included.

1.8.6 Exclusion criteria

Patients on acute dialysis were excluded. These included patients receiving dialysis for acute renal failure and those with chronic renal failure who were on temporary dialysis but not yet accepted to the chronic program. The unit does not exclude patients solely on age.

1.8.7 Data collection and statistical analysis

Data was obtained from patient's transplant work-up files, which are maintained in the renal unit. Information regarding demographic features, disease profile, year of initiation of dialysis, year of presentation for transplantation (collected under "other information" as not all patients were presented), listing for transplantation (as only patients who are accepted at presentation are listed for transplantation), HIV status (including CD4 and Viral load if positive), and transplant readiness was collected. All data was captured on an excel data sheet (Appendix D) and entered into Redcap. Stata was used for statistical analysis. Continuous data was tested for normality. Where applicable the data is presented as medians and range or mean and standard deviation. Students T-test was used to test differences between groups for continuous variables. Categorical data is presented as proportions and frequencies. The Chi-squared test was used to assess the relationship between categorical variables, and if the frequency was ≤ 5, a Fisher's exact test (two-tailed) test was used. All data was analysed at a 95% confidence interval and a p value of <0.05 was reported as significant.

1.8.8 Parameters

Data was collected for the following parameters:

- Demographic features
- Dialysis modality and year of initiation of dialysis
- Investigations undertaken for transplant eligibility (whether acceptable for transplant or not)
- Transplant information
    - Qualifies
    - Year Presented (collected under "other info" on data sheet)
    - Listed
    - Suspended (Reason for suspension collected under "other info" on data sheet)

See Appendix D for details

1.9 Limitations

The following limitations were identified in this study:

- Small sample size
- Cross sectional study (prospective study may yield more information)
- Patient population studied is representative of the population groups in the drainage area of Helen Joseph Hospital, a public sector institution. These figures are therefore not representative of SA's demographic features and may not accurately reflect private sector experience.
- No information is available on transplanted patients from Helen Joseph Hospital as their care is handed over to Charlotte Maxeke Johannesburg Academic hospital. Unfortunately, the unit does not keep records on the specific dates that patients have undergone transplants

1.10 Ethical considerations

Confidentiality of information regarding all patients as well as their medical records was safeguarded through the use of numbering to record each subject. Patient names were not used on any data collection sheets and the links between the data and patient names were kept separate. The data collection sheets were kept in a secure location after entering into an electronic data sheet. Due to the nature of this study, no consent was required from patients. Written approval and permission was obtained from the Head of the Renal Unit at Helen Joseph Hospital as well as the Superintendent and the Human Research Ethics Committee of the University of the Witwatersrand (Appendix F Clearance certificate number: M160906).

1.11 Project outline

1.11.1 Costs

Costs were covered by the researcher.

1.11.2 Time Frame

	2016					2017					
	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Literature Review											
Preparing protocol											
Protocol Assessment											
Ethics Application											
Collecting data											
Data Analysis											
Writing up thesis											
Writing up paper											

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CHAPTER 2: Submissible Article

Title: **The use of chronic dialysis in a resource-poor environment: demographic features and transplant readiness at Helen Joseph Hospital Renal Unit**

Authors:
D Parbhoo MBBCh (Wits), Dip HIV Man (SA), FCP (SA)

Affiliations: D Parbhoo
Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand.

Conflict of interest: Nil

Keyword: Chronic Dialysis, Chronic Renal replacement South Africa, Dialysis Unit

Corresponding Author:
Dr Dinen Parbhoo
Email: dinenparbhoo@gmail.com

Word Count: 4625
Abstract: 404

ABSTRACT

Background

Chronic kidney disease (CKD) places a considerable economic strain on health care systems. In South Africa resource limitations in the public sector mandate that patients with end stage renal disease (ESRD) are only offered dialysis if they qualify for renal transplant. Thus, chronic dialysis serves as a bridge to transplantation.

Objectives

The primary objective of this study was to describe the patients on the chronic dialysis program with regards to demographic features, aetiology of renal failure, associated chronic co-morbidities and transplant readiness. Secondary objectives included the determination of the type and duration of dialysis used and the documentation of any possible differences between the haemodialysis (HD) and peritoneal dialysis (PD) groups and the HIV positive and negative patients.

Methods

A cross-sectional record review was conducted of all patients receiving chronic dialysis at the Helen Joseph Hospital's Renal Unit as at September 2016. Information regarding demographic features, disease profile, year of initiation of dialysis, year of presentation, Human Immunodeficiency Virus (HIV) status and transplant readiness was collected. All data was analysed at a 95% confidence interval and a p value of <0.05 was considered significant.

Results

There were 92 patients on chronic dialysis, 46 each on PD and HD. The mean (SD) age of patients in this study was 43.8 years (10.8). There was a slight female predominance (51.1%). The predominant ethnic group was African (64.1%). The leading causes of ESRD were hypertension (35.9%) followed by diabetes mellitus (10.9%). The most frequent comorbidity was hypertension (98.9%) followed by HIV infection (36.1%). The median time that patients spent on dialysis before presentation for transplant listing was 2 years (range 0-9 years). At the time of analysis, 27 patients (29.4%) were eligible for transplant and 38 patients (41.3%) were in the process of transplant eligibility evaluation. Twenty-seven patients (29.4%) were ineligible for transplant. Of those eligible for transplant, 21 were listed for transplant and 6 were awaiting presentation for listing. There were no differences between the HD and PD groups or the HIV positive and negative groups with regards to qualification for transplant.

Conclusion

The demographic features and underlying aetiologies of our cohort are similar to national figures with only the racial composition being different. The proportion of patients listed for transplantation (22.8%) and median time for work-up (2 years) are both sub-optimal. Improved efficiency in the evaluation of transplant eligibility is required in order to optimize the appropriate allocation of dialysis in a resource-limited setting.

Introduction

"Superficially, it might be said that the function of the kidneys is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself" (1).

Chronic Kidney Disease (CKD) is defined as abnormality of renal function with an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2 or urinary albumin excretion of >30 mg/day, for more than 3 months. End stage renal disease (ESRD) is defined as an eGFR <15ml/min/1.73m^2 (2, 3).

Chronic kidney disease is a global health problem, placing an economic burden on all countries (4-7). Global life expectancy had increased from 61.7 years in 1980 to 71.8 years in 2015 (8, 9). In the resultant aging population, non-communicable diseases like CKD have become more prevalent (8, 9). Deaths from CKD have risen by 31.7% from 2005 to 2015 and CKD is now the 12th most common cause of death worldwide (9).The prevalence of CKD is estimated at 13.4% globally, closely resembling data from Sub-Saharan Africa at 13.9% (8). However, in Sub-Saharan Africa less than five percent of patients with ESRD will receive renal replacement therapy (RRT) (10).

In developing countries rapid urbanization, poor diet and inactivity have contributed to the increasing prevalence of obesity, hypertension and diabetes (11). This has resulted in an increase in CKD (11). In low to middle income countries, inadequate risk factor management in patients with CKD brought about by lack of adequate screening systems and insufficient numbers of qualified specialists contributes to the increased burden of ESRD (9, 11). In these countries, access to RRT is often limited due to financial and resource constraints (7).

In Sub-Saharan Africa, the increasing rate of non-communicable diseases is exacerbated by the large burden of communicable diseases. Sub-Saharan Africa has more than 22 million people living with HIV (12). In addition to the well-described renal diseases associated with HIV infection, improved survival of HIV-affected patients resulting from improved access to appropriate treatment increases the risk for the development of ESRD due to causes other than HIV itself (12-15). Furthermore, ESRD is seen in younger adults between 20-50 years of age and is primarily due to hypertension and glomerular disease (16). In developed countries it is seen largely in the middle aged to elderly population due to hypertension and diabetes (17).

In 2015 the population of SA was estimated to be 54.96 million (18). The World Bank regards SA as an upper-middle income country; however, significant disparities exist in per capita income due to historical inequalities. Approximately 62-72% of the population relies solely on public health care and only 28-38% have access to private health care (8, 18). There are also large disparities in terms of access to renal dialysis units based on geographical location in SA. The 2013 and 2015 Annual Report from the South African Renal Registry notes that the provinces of Limpopo and Mpumalanga do not have any state-funded treatment centres (18, 19). Transplant centres are only available in 4 of the 9 provinces (18, 19).

Transplantation is the ideal form of RRT as it improves the quality of life (physical, mental, emotional and social functioning) and reduces the mortality risk for most patients (3, 20-22). In a systematic review, 76% of studies found a lower risk of death in transplant patients compared to those on dialysis (22). Transplantation also reduced the risk of cardiovascular events such as myocardial infarction, stroke, ischaemic heart disease and heart failure (22). There was a reduced rate of infection amongst transplant patients despite immunosuppressive therapy (22). Even though there is an increased short term (0-3 months) risk of death after transplantation due to the surgery itself and immunosuppressive therapy, the long term survival is increased when compared to patients on chronic dialysis (23).

Current SA guidelines for RRT in the public sector indicate that eligibility for transplantation determines acceptance for dialysis due to financial and resource constraints (24). The estimated cost of RRT is ZAR 200 000.00 per person per year (10). Patients requiring RRT are evaluated by individual renal units and stratified according to suitability for transplantation (25). At present, in the public sector, most renal units are at full capacity for chronic dialysis slots (25, 26).

Whilst the South African Renal Registry's annual reports of 1994 and 2015 indicate a marked increase in the absolute number of patients on RRT, this is largely due to improved capacity in the private sector (18, 19, 27). In addition, the transplantation rate has fallen from 8.7 per million population (pmp) in 1994 to 4.6 pmp in 2015 with the absolute number of renal transplants performed in 1994 being 299 compared to 254 in 2015 (18, 27). This may be due to the high cost of performing the transplantation and a shortage of organ donors.

There are currently 4300 listed patients awaiting different organ transplants in SA (28). In 2016, 37% of kidney recipients were related to the donor thus leaving 63% dependent on other living

or cadaveric donors (28). Renal replacement in SA has not increased proportionally to the population growth and the current infrastructure is unable to cope with the growing burden of ESRD (18, 29).

The objectives of this study were to describe the patients on the chronic dialysis program with regards to demographic features, aetiology of renal failure, associated chronic co-morbidities and transplant readiness. To determine the type and duration of dialysis used and to document possible differences between the HD and PD groups and the HIV positive and negative subgroups

Methods

A cross-sectional record review was conducted of all patients receiving chronic dialysis at the Helen Joseph Hospital's Renal Unit as at September 2016. The Helen Joseph Hospital is a regional academic hospital complex, together with Rahima Moosa Mother and Child Hospital, situated in Newclare, Johannesburg. Helen Joseph Hospital is exclusively an adult hospital and thus there were no paediatric patients in the study.

Data was obtained from patient's transplant work-up files, which are maintained in the renal unit. Information regarding demographic features, disease profile, year of initiation of dialysis, year of presentation for transplant (collected under "other info" as not all patients were presented), whether the patient was listed for transplantation (as not all patients presented are accepted onto the transplant list), HIV status (including CD4 and Viral load if positive), and transplant readiness was collected. Medical conditions such as hypertension or HIV could be either a cause or a co-morbid condition associated with CKD. For the purposes of this study, this was determined by the opinion of the nephrology team at the initiation of the patient onto the chronic dialysis program (which was recorded in the transplant file). Blood investigations were performed according to the guidelines by the SA Renal Society (Appendix E) (20). The haemoglobin was done monthly. CD4 and viral loads four monthly (January, May and September). Blood grouping and antibody testing are done at the time of listing.

All data was captured on a data sheet (Appendix D) and entered into Redcap. Stata was used for statistical analysis. Continuous data was tested for normality. Where applicable the data is presented as medians and range or mean and standard deviation. Students T-test was used to test differences between groups for continuous variables. Categorical data is presented as

proportions and frequencies. The Chi-squared test was used to assess the relationship between categorical variables and if the frequency was ≤ 5, a Fisher's exact test (two-tailed) test was used. All data was analysed at a 95% confidence interval and a p value of <0.05 was reported as significant.

Results

Demographic features

At the time of data collection, there were 92 patients receiving chronic dialysis, 46 each on peritoneal dialysis (PD) and haemodialysis (HD). Eight patients had changed from PD to HD due to the development of peritonitis. Two patients changed from HD to PD due to patient preference. Both these changes occurred prior to the time of data collection. There was a slight female predominance (51.1%). The majority of patients were Black/ African (64.1%). The mean (SD) age of patients in this study was 43.8 years (10.8) (Table 7).

ESRD aetiology and co-morbid disease profile

The causes of ESRD were noted to be hypertension in 33 (35.9%), diabetes in 10 (10.9%), glomerulonephritis in 8 (8.7%), polycystic kidney disease in 5 (5.4%) and HIV in 3 (3.3%) patients respectively. Other causes included obstructive uropathy in 3 (3.3%) and severe acute renal failure from various causes (toxins and overdose) in 4 (4.3%) patients respectively. The cause was unknown in 32 patients (34.8%) (Figure 2). No significance difference was noted in the aetiologies between the HD and PD groups (Table 9).

The most frequent co-morbid illness was hypertension in 91 patients (98.9%). Twenty-five patients (27.2%) had HIV and 11 (12%) had diabetes mellitus. The majority of patients had more than one co-morbidity (Figure 3).

Transplant workup

BMI was only recorded in 34 patients (37%) as the relevant data was not available for the rest of the patients. The median BMI was 25.0 kg/m^2 (Range 18.25-39). A total of ten patients had BMI's greater than 30 kg/m^2, five in HD and five in the PD group. Five patients had BMI's greater than 35kg/m^2, two in HD and three in the PD group. There was no difference between the two groups in terms of BMI (p= 0.46).

Laboratory investigations

Ninety patients (97.8%) were tested for Hepatitis B and C; all were negative for both infections. Hepatitis B and C are not exclusion criteria at Helen Joseph Hospital Renal Unit.

Twenty-five patients (27.2%) were HIV positive and all were on antiretroviral therapy. The median CD4 count was 430 (range 8- 2 737). There were 22 patients (88%) with CD4 counts above 200 cells/ųl. Nineteen patients (76%) had viral loads less than 1000 copies/ml and of those, 14 were undetectable (based on the laboratory referenced used).

ABO grouping was done in 41 patients: 16 patients (39%) were blood group O, 15 patients (36.6%) were blood group A, 10 patients (24.4%) were blood group B and no patients tested were blood group AB. Rhesus (Rh) blood grouping was performed in 33 patients: of these 24 (72.7%) were Rh positive and 9 (27.3%) were Rh negative.

Specialized blood testing prior to transplantation: presence of antibodies to human leukocyte antigen (HLA) molecules (HLA class I and/or class II), were only done in 30 patients (32.6%). Pre-transplantation panel reactive antibody (PRA) estimation was only done in 31 patients (33.7%).

Core Investigations

An electrocardiogram (ECG) was done in 79 patients (85.9%), of these, one was not acceptable, needing further cardiac evaluation.

Echocardiographic findings were recorded in 80 files (87%) and 72 patients (90%) did not have any exclusion features. Abdominal ultrasonography reports were obtained in 75 patients (81.5%), 73 of these were acceptable (97.3%) and two had exclusion criteria.

Gastroscopy was performed in 75 patients (81.5%), only one patient had an exclusion criterion on gastroscopy.

A voiding cysto-urethrogram (VCU) was performed in 63 patients (68.5%); four of these patients needed further urological intervention in order to be deemed acceptable for transplant and 29 patients (31.5%) were still awaiting the investigation.

Further investigations for select groups

Carotid Doppler ultrasonography was performed in 19 patients; one was not acceptable for transplant due to the presence of excessive atherosclerosis.

An exercise stress test was performed in 11 patients, all were acceptable for transplant. Coronary angiography was required in 4 patients and all were acceptable.

There were 47 female patients, however a Pap smear was only available in 29 patients (61.7%), one patient required further gynaecological intervention.

Duration on dialysis prior to presentation for transplantation

Fifty-nine (64.1%) patients had not been presented for transplantation at the time of data collection, thus their duration on dialysis was calculated from the time of initiation of dialysis to the time of data collection. The median duration on dialysis in this group was 1 year (Range 0-14 years). The PD group accounted for 32 of these patients with a median duration of 1 year (Range 0-8 years). In the 27 patients on HD awaiting presentation the median duration on dialysis was 3 years (Range 0-14 years).

Thirty-three (35.9%) patients had been presented for transplantation. Their duration on dialysis was calculated from the time of initiation on dialysis to the year presented. The median duration from initiation of chronic dialysis to presentation in these patients was 2 years (Range 0-9 years). The HD group accounted for 19 of these patients with a median of 2 years to presentation (Range 0-8 years), the PD group accounted for the remaining 14 patients, with a median of 2.5 years to presentation (Range 0-9 years).

Qualification for transplant

Of the study cohort, 27 patients were eligible for transplantation (29.4%). Of these patients, 21 (77.8% of patients eligible for transplant and 22.8% of all patients on dialysis) were listed and 6 (22.2% of patients eligible for transplant and 6.5% of all patients on dialysis) were awaiting presentation and listing (Figure 4).

Twenty-seven patients (29.4%) were ineligible for transplantation at the time of data collection. Three patients (3.3%) had completed their pre-transplant evaluation, but were not yet presented, one was suspended due to poor compliance to treatment and the other two patients had elevated BMI's and needed to lose weight before presentation.

Twelve patients (13.0%) were previously presented for transplantation and subsequently suspended. Four patients in this group had been permanently excluded from future transplantation: due to the development of severe bronchiectasis in one, ischemic heart disease in another and another two deemed medically unfit for transplantation at discussion at the transplant meeting (due to progression of underlying cardiovascular disease). The other eight needed further investigation and re-presentation, the reasons for which include: development of peritonitis, uncontrolled HIV disease, development of a new medical condition requiring further evaluation (e.g. recurrent pleural effusions, upper gastrointestinal bleeding). Two patients needed repeat cardiac evaluation due to echocardiogram investigations being more than three years old. One patient required a parathyroidectomy for the development of tertiary hyperparathyroidism and the last patient was suspended due to habitual non-compliance to treatment and follow up.

Twelve patients (13.0%) were found to have permanent exclusion criteria during the pre-transplant evaluation (thus never presented). Some patients had advanced co-morbid illnesses such as: three patients with significant cardiac disease with low ejection fractions; one patient with advanced chronic lung disease; one patient with liver cirrhosis with portopulmonary hypertension; one patient with significant cerebrovascular disease with multiple strokes and one with uncontrolled psychiatric disease. Two patients were foreigners (who do not qualify for transplantation in the state sector). One patient was morbidly obese and needed to lose in excess of 20 kilograms in order to meet the BMI criteria for transplantation and two patients were excluded due to habitual non-compliance to treatment and follow-up.

There were 38 patients (41.3%) in whom the transplant eligibility was unknown at the time of data collection as the workup was incomplete.

In the HD and PD groups there was no difference with regards to qualification for transplant. In the HD group 16 patients were eligible for transplantation, 14 were ineligible, and 16 had an incomplete workup. In the PD group 11 were eligible for transplantation, 13 were ineligible and 22 had an incomplete workup.

A further analysis was done comparing HIV positive and HIV negative patients. There was no difference between the groups with regards to: eligible for transplant ($p= 0.53$), ineligible for transplant ($p=0.46$) and those with an incomplete work up ($p=0.53$).

Type of Donor

Only 4 of the 41 patients (9.8%) who had been counselled by the transplant team had an identified related living donor for work-up.

Discussion

Demographic features

The mean (SD) age of patients in this study was 43.8 years (10.8). This was similar to a previous study at Chris Hani Baragwanath Hospital in 2012 which had a mean (SD) age of 45 (13) years (30). It is also in keeping with national statistics from the 2015 South African Renal Registry report that noted a mean (SD) age of 43.4 (13.5) years in the public sector, which was lower than in the private sector. The lower mean age in the public sector is due to the strict selection criteria applied where younger people are more likely to be accepted for dialysis (18, 25).

In Sub-Saharan Africa the mean age of patients with CKD is 41.4 years (12). This is in contrast to developed countries where the prevalence of ESRD was highest in the 65 to 74 year age group in the USA and in the UK the median age at the start of HD was 66.8 years and PD at 60.5 years in 2016 (31, 32). The differences in age between this study and developed countries can be explained by the differences in selection criteria applied and aetiology.

Females accounted for 51.1% of the study population. This was in keeping with the national population census of 2015 and a study conducted on chronic dialysis patients at Tygerberg Hospital in the Western Cape where 64.2% of the patients were female (33, 34). However, this is inconsistent with the 2015 South African Renal Registry Report, which showed a male predominance with only 40.7% of patients being female (18). Data from global renal registries showed a male dominance of 57.8% in the USA, 62.9% in the UK and 70.3% in India (31, 32, 35).

The study had a majority of Black/African patients (64.1%), 25% Coloured/ Mixed ethnicity, 6.5% Indian and 4.3% White. This ethnic breakdown was different to the 2015 national census, which reported 80.5% Black/African, 8.8% Coloured/Mixed ethnicity, 8.3% White and 2.5% Indian people (33). However, the racial profile of the study patients is a representation of the racial profile of the community that the hospital serves.

Aetiology of ESRD

In the study the most frequent cause of ESRD was hypertension (35.9%) with diabetes accounting for 10.9%. The aetiologies in this study closely resembled those in the 2015 Renal Registry Report: hypertensive renal disease 33.7%, diabetic nephropathy 14.4%, glomerular disease 9.5%, cystic kidney disease 2.9%, obstruction and reflux 1.5% and unknown in 34.1% (18). In SA, 30.4% of the adult population have hypertension (36, 37). There is an increased prevalence of hypertension in urban versus rural Africans attributed to the consumption of excess salt, increased stress levels and decreased physical activity (38). In a study to evaluate the pathological basis of ESRD in African patients, essential malignant hypertension was the histological diagnosis in 49%, which was most prevalent in the 41-50 year age group (39). In the local setting, renal biopsies are not routinely performed on all patients with ESRD, hence the actual prevalence of hypertension may be higher than reported in this study.

This is in contrast to developed countries where the leading cause of ESRD is diabetes, which typically affects an older population (31, 32). In some developing countries, such as Libya and India, diabetes is also the most frequent cause of ESRD and this is primarily due to genetics, physical inactivity, obesity and diet (35, 40).

Co-morbid illnesses

Hypertension was noted in 98.9% of patients, however it was only recorded as a primary cause of ESRD in 35.9%, this is due to secondary hypertension caused by ESRD. Of the 22 patients with diabetes mellitus, only one had ESRD from an unrelated cause. Twenty-five patients (27.2%) had HIV, however, HIV-related kidney disease was recorded as the cause of ESRD in only 3 patients (3.3%). This has been noted in other studies, which have shown that as people with HIV live longer, they too are at risk of ESRD from causes other than HIV (12, 13).

Duration on dialysis prior to presentation for transplantation

Fifty-nine (64.1%) had never been presented for transplantation. This subgroup included six patients fully worked up and awaiting presentation, three patients who were suspended before presentation and 12 patients who were found to have permanent exclusion criteria to renal transplantation during work-up and thus never presented. However, in the remaining 38 patients, the reason for outstanding investigations included long waiting periods for certain investigations and in some, appointments were being missed and thus investigations not being done. Haemodialysis patients spend 3 days of the week at the hospital as compared to PD

patients, who generally follow up once a month. Thus, the HD group, who spends more time at the hospital, should be able to honour their follow up appointments for pending investigations.

Thirty- three (35.9%) patients had been presented for transplantation. The median duration from initiation of chronic dialysis till presentation was 2 years (Range 0-9 years), with no difference between the HD and PD groups.

Transplant work-up and presentation

Only 34 of the study cohort had a BMI recorded. Ten patients (10.9%) had BMIs greater than 30 kg/m^2. Data from the South African Demographic and Health Surveys between 1998 and 2016 indicate that the prevalence of obesity (BMI ≥30kg/m^2) in adults (>15 years of age) had risen in males from 9% to 11% and in females from 27.4% to 41% (41, 42). This study had five patients (5.4%) with BMI's greater than 35kg/m^2. Of these patients, three were suspended (solely due to BMI) either before or after presentation. One patient still had an incomplete workup and one patient was permanently suspended due to both BMI (36kg/m^2) and medical conditions.

According to The European Best Practice Guidelines, patients with a BMI above 30 kg/m^2 are advised to lose weight before consideration for transplant, due to the increased risk of complications post transplantation (43). South African Guidelines state that a BMI greater than 35 kg/m^2 is an exclusion factor for transplant, due to an increased rate of complications post-transplant and shorter graft survival (20). This explains the lower prevalence of obesity seen in the study population.

In this study 21 patients (22.8%) were listed for transplantation, compared to CHBAH where 43.8% of patients on chronic dialysis were listed. The renal unit at CHBAH has 160 patients on dialysis of whom 95 are on HD and 65 on PD. Seventy patients are on the transplant list, 73 patients awaiting listing (which included patients that had an incomplete workup) and 17 were non-transplantable (personal communication, 17 September 2018: Appendix C). It is a larger tertiary academic hospital, with more nephrologists, cardiologists, radiologists and allied health care workers. This could be the reason that investigations are performed timeously, and more patients are presented.

The transplant work-up was incomplete in 38 patients (41.3%). In this group, simple investigations such as an ECG, Echocardiogram, pap smear, VCU and abdominal ultrasound

were pending. This is due to the various reasons mentioned above. In an ideal setting with adequate access to health care, referral to a nephrologist in early stage CKD, risk factor management and appropriate medical therapy, the transplant evaluation can be done prior to the development of ESRD.

The longer patients wait to presentation, the further this prolongs their time to possible transplantation and results in increased cardiovascular morbidity and mortality. This may lead to permanent exclusion from transplantation, of patients who are on already on the chronic dialysis program. These compound the problem of having patients on the chronic dialysis program who are not transplantable, leading to a greater financial burden.

In the USA, in 2016, the median waiting period from listing to first transplantation was 3.6 years (44). Data from the UK transplant registry shows that the median waiting time from listing to transplantation is 2.3 years (45). These waiting periods are a function of organ availability rather than access to transplantation facilities. There is no published data available on duration from the start of dialysis to presentation for transplantation in South Africa.

In this study 27 patients (29.4%) were ineligible for transplantation. A total of 16 patients (17.4%) had permanent exclusion criteria for transplantation (12 prior to presentation and four after presentation). There was no difference when compared to data from CHBAH, where 10.6% of their patients were non-transplantable (p=0.17). A study conducted at Erasme University hospital in Belgium found that 8% of patients referred for transplantation evaluation between 2001 and 2006 were deemed ineligible due to medical contraindications (46).

There were various reasons for suspension, some of which were temporary- such as patients who had become obese since presentation (BMI's above 35 kg/m^2) and outdated investigations (ECG/ echo older than 3 years). However, some were irreversible, such as development of a cardiomyopathy, progression of vascular disease and development of bronchiectasis and resulted in permanent exclusion. This poses an ethical dilemma. Stopping dialysis in these patients would be against the principle of non-maleficence. However, to continue would result in blocked dialysis slots, which could be used for someone who qualifies for transplantation (distributive justice). In Sub-Saharan Africa, less than 5% of patients with ESRD will receive RRT. In a resource poor country, this dilemma will always be present, and currently there are no clear guidelines on the procedure to follow.

Type of Donor requested

Forty-one patients had been counselled on type of donor for transplantation. Only four (9.8%) had recruited a related living donor. This is in comparison to the SA organ donor foundation report of 2016, where 37% of kidney recipients were related to the donor (most within the private sector). This leaves a large proportion of patients in this study dependent on cadaveric donors. India has reported rates of living donor transplantation as high as 90% and only 10% from cadaveric donors and is currently the second largest living kidney transplantation program after the USA (47). Thus, if patients have possible related living donors, this may shorten the duration from presentation to transplantation and improve our transplantation rates.

Strengths and weaknesses

The strengths of the study include identification of possible areas for improvement within our renal unit, in order to streamline the process from development of ESRD to work-up to presentation and transplantation. Inter-departmental collaboration, with allocation of dedicated time slots or prioritization for investigations to be done for renal pre-transplant evaluation, may improve the efficiency of the transplant work-up. Greater emphasis needs to be placed on patients with CKD before they require dialysis, which may allow a longer time frame to perform the recipient transplant evaluation. Improved counselling strategies need to be implemented in order to promote the identification of related/altruistic living donors, which may help improve our transplantation rates.

The limitations included the study methodology, as it was a cross sectional study (a prospective study may yield more information). There was a small sample size, however these were the only available slots and number of patients the unit can support. The patient population studied is representative of the population group in the drainage area of Helen Joseph Hospital and therefore not representative of SA's demographic features. Other limitations included poor record keeping, resulting in some fields of data being incomplete, such as BMI not being recorded in the files of all patients.

Contribution to the body of knowledge

Currently, there is no published data in SA on the completeness of transplant work-up of patients, nor the eligibility for transplantation of patients on chronic dialysis. Prior to this study, there was no formal audit of the patients on chronic dialysis at Helen Joseph Hospital.

Conclusion

The demographic features of our cohort are similar to national figures with only the racial composition being different (due to the site of the study). Hypertension and diabetes were common underlying aetiologies, this is consistent with the national figures. The proportion of patients listed for transplantation (22.8%) and median time for work-up (2 years) are both sub-optimal. Improved efficiency in the evaluation of transplant eligibility is required in order to optimize the appropriate allocation of dialysis in a resource-limited setting and improve transplantation rates.

Further research is needed to identify reasons for incomplete work-up and address these at the Helen Joseph Renal Unit. Audits in other units in SA will help to identify problems and eventually may improve access to RRT.

Table 7: Demographic features of patients on chronic dialysis

		Total n=92	Haemodialysis n=46	Peritoneal dialysis n=46	p value (HD vs PD)
Age (years) Mean (SD)		43.8 (10.8)	43.2 (11.4)	44.5 (10.2)	0.56*
Gender Number (%)	Male	45 (48.9)	24 (52.2)	21 (45.7)	0.67**
	Female	47 (51.1)	22 (47.8)	25 (54.3)	
Race Number (%)	African	59 (64.1)	29 (63)	30 (65.2)	1.00**
	White	4 (4.3)	3 (6.5)	1 (2.2)	0.62**
	Indian	6 (6.5)	3 (6.5)	3 (6.5)	1.00**
	Coloured	23 (25)	11 (23.9)	12 (26.1)	1.00**

*Student's (Unpaired) T Test

**Fisher Exact test

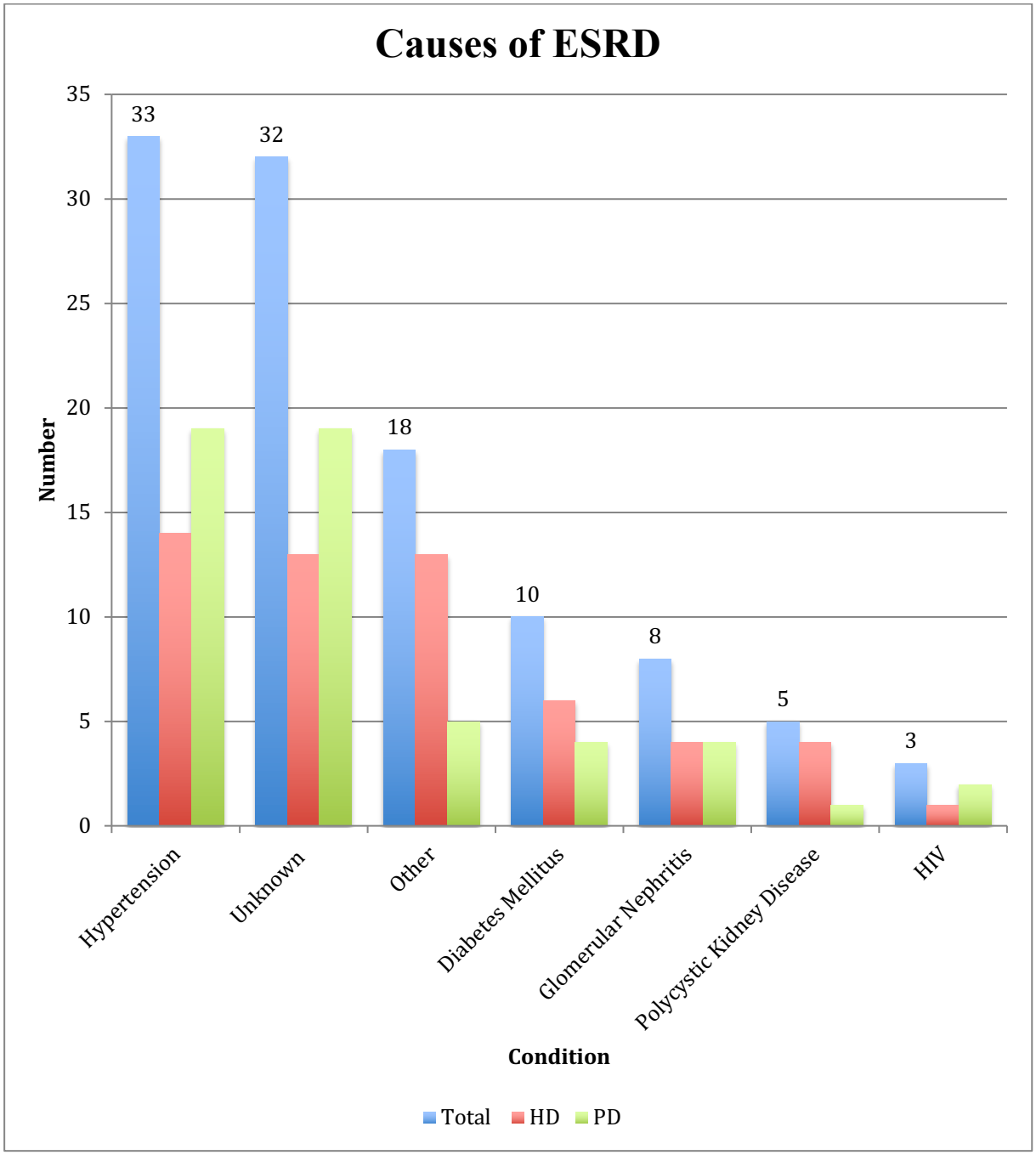

Figure 2: Causes of end stage renal disease

Table 8: Aetiologies of end stage renal disease comparing patients on haemodialysis and peritoneal dialysis

Aetiology	Haemodialysis	Peritoneal dialysis	p value*
Hypertension	14 (30.4%)	19 (41.3%)	0.38
Diabetes	6 (13%)	4 (8.7%)	0.74
Glomerulonephritis	4 (8.7%)	4 (8.7%)	1
Polycystic kidney disease	4 (8.7%)	1 (2.2%)	0.36
HIV	1 (2.2%)	2 (4.3%)	1
Unknown	13 (28.3%)	19 (41.3%)	0.27
Others	13 (28.3%)	5 (10.9%)	0.06

*Student's T Test

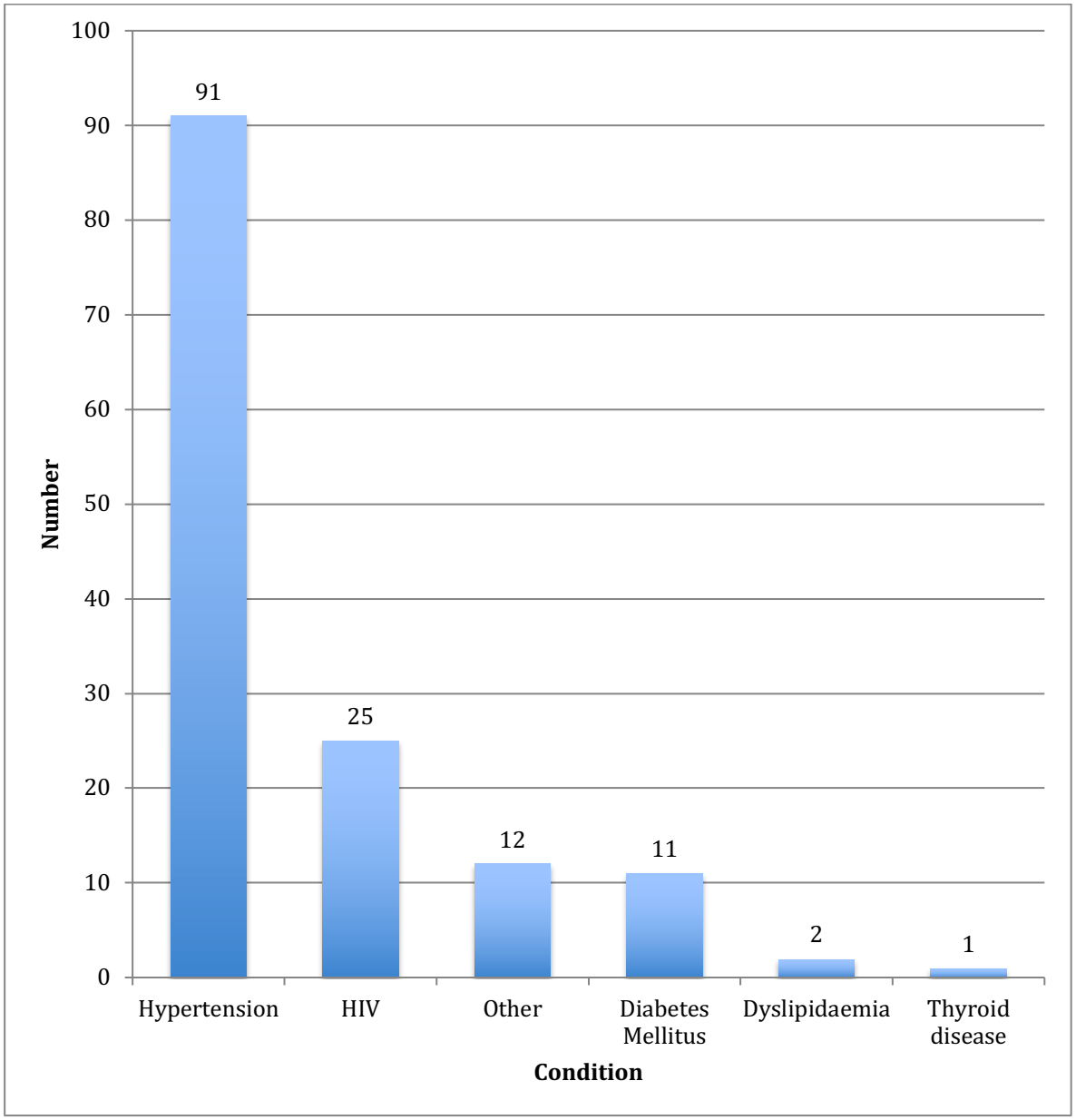

Figure 3: Co-morbid conditions

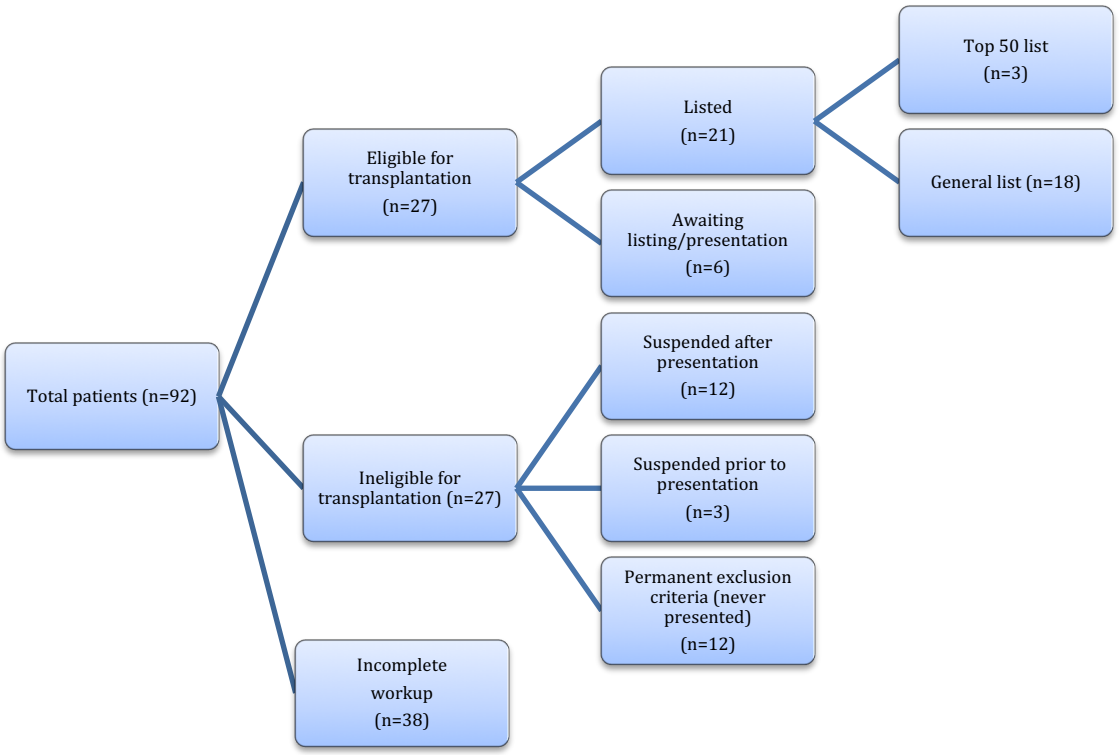

Figure 4: Eligibility for transplantation

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CHAPTER 3: Appendices

1.13 Appendix A Exclusion criteria from Department of Heath guidelines

3. EXCLUSION CRITERIA

Exclusion rather than inclusion criteria should be applied for the selection of a suitable patient.

Before it is decided that dialysis is a suitable option for an individual there should be a full assessment of the patient's healthcare needs such as economic, social, school and work circumstances. The consequences of long- term dialysis are significant on the patient and their families.

3.1 Medical exclusion criteria

- Active, uncontrollable malignancy or with short life expectancy
- Advanced, irreversible progressive disease of vital organs such as:
  - cardiac, cerebrovascular or vascular disease
  - advanced cirrhosis and liver disease
  - medically or surgically irreversible coronary artery disease
  - lung disease
  - unresponsive infections e.g, HPV, Hepatitis B and C
- HIV and AIDS are not a medical exclusion criteria provided the patient has access to a comprehensive AIDS treatment plan including antiretroviral treatment and stable for at least six months and the above exclusion factors are absent.

03

- Age (provided above exclusion factors are absent) is not a contra-indication for chronic renal dialysis. In the UK the median age of starting renal replacement therapy is 63 years and the median age of the population is 54 years.

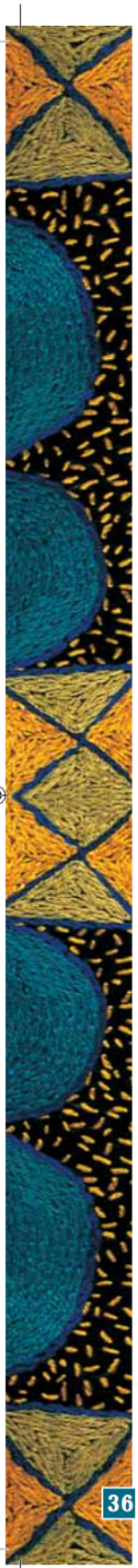
3.2 Psychological Exclusion Criteria

- Any form of mental illness that has resulted in diminished capacity for patients to take responsibility to their actions.
- Active substance abuse or dependency including tobacco use.
- Obesity

3.3 Compliance

- Patients with proven habitual non-compliance with dialysis treatment and lifestyle modification will be excluded or removed from chronic renal dialysis programme

1.14 Appendix B Criteria for HIV infected patients



vidual basis to determine whether dialysis will be offered. This will depend on the following considerations:

- Does the patient have acute reversible renal failure?
- What is the short-term prognosis of the patient?
- What is the availability of treatment at the centre?
- Would the patient be able to reconstitute his immune system? This may depend on several things including CD4 count, previous HAART, compliance and disease complications.
- Does the patient have a contraindication to renal transplantation, e.g. lymphoma?

2. GUIDELINES FOR MANAGEMENT OF KIDNEY TRANSPLANTATION IN HIV-INFECTED PATIENTS

2.1 INTRODUCTION

Before the introduction of HAART the morbidity and mortality of HIV-infected patients were considered to be too high to justify using scarce resources in transplanting infected patients. There were concerns that immunosuppression may accelerate HIV replication and result in rapid progression of the disease and increased mortality. Most reports on the effects of immunosuppressive agents (cyclosporine and mycophenalate mofetil) *in vitro*, on non-transplant HIV-infected patients and in HIV-infected transplant patients, have not shown detrimental effects and have in fact suggested that there may be beneficial effects.

2.2 MAIN RECOMMENDATIONS

All HIV-infected patients with CKD should be considered for RRT, including dialysis and transplantation.

Before listing for transplantation HIV-infected patients must demonstrate:

- Stability on HAART therapy with good adherence to treatment for at least 6 months.
- Absence of current AIDS-defining illness.
- CD4 count >200/µl for more than 6 months.
- Paediatric criteria:
  - <1 year of age – aim to get to 1 year or 10 kg before transplantation if possible
  - 1 - 6 years – CD4% >25% (but also consider absolute count)
  - >6 years – CD4 >200.
- Undetectable viral load (<50 copies/ml) for more than 6 months.

2.3 IMPORTANT CONSIDERATIONS

It has been well established that compliance with medication and clinic attendance is essential for successful management of both HIV infection and kidney transplantation. It is recommended that:

- Patients must be able and willing to attend close and regular follow-up.
- Patients must be willing to comply with antiviral and antifungal prophylaxis regimens.
- Patients must have a negative pregnancy test and be willing to use effective contraception for at least 2 years post-transplant.
- Women must have annual Pap smears before transplant, as well as mammograms.
- Adolescents will need extra support.
- Patients need to agree to be sent to a centre where a multidisciplinary approach including HIV specialists, nephrologists, dietitian and pharmacology support is available.

2.4 EXCLUSION CRITERIA

- Advanced cardiopulmonary disease
- Active uncontrolled malignancy with reduced life expectancy (see national guidelines for solid organ transplantation)
- Significant infection that may flare up or reactivate with immunosuppression (aspergillosis and other fungal infections, severe bacterial disease and active TB)
- Active human papillomavirus infection
- Evidence of liver cirrhosis (especially if co-infected with hepatitis B or hepatitis C virus)
- Untreated hepatitis B or hepatitis C co-infection with active viral replication – consider treatment for hepatitis B or hepatitis C first
- Documented progressive multifocal leukoencephalopathy
- Kaposi's sarcoma
- EBV and human herpesvirus 8 (HHV8)-associated lymphoproliferative diseases
- Active CMV
- Documented poor compliance.

2.5 HIV-RELATED CRITERIA FOR RENAL DIALYSIS AND TRANSPLANT PROGRAMMES

HIV infection should not be a reason for exclusion from renal dialysis or renal transplant programmes *per se*. However, like patients with other medical conditions the HIV-infected patient with ESRD needs to be assessed in terms of co-morbidities and psychosocial factors for suitability for these programmes.

Renal transplantation should only be undertaken in HIV-infected patients when the following criteria are met, in order to optimise the outcome after transplantation:

1. Patient on antiretroviral therapy (ART) for at least 6 months.
2. Adherence to ART is demonstrated and there is a commitment to lifelong therapy.
3. CD4 count >200 cells/µl.
4. HIV viral load undetectable.
5. No active opportunistic infections (OIs). If the patient has had a WHO stage 4 infection or TB they should have been fully treated and have been asymptomatic from this infection for at least 6 months.
6. No history of malignancies. However, if the patient has had a previous solid tumour that has been adequately treated and is now in remission they may be considered if they meet criteria for sufficient duration of remission prior to transplantation for HIV-uninfected patients (consult IPTTR prelisting).
7. Absence of certain HIV-related conditions:
   a. History of progressive multifocal leucoencephalopathy (PML)
   b. History of EBV or HHV-8-associated lymphoprolif-

1.15 Appendix C Permission letter from CHBAH Nephrology HOD

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Chris Hani Baragwanath Academic Hospital
Dr Mduduzi Mashabane
Head of the Division of Nephrology
Department of Medicine
University of the Witwatersrand
Tel. no.: (011) 933-9374
Fax no.: (011) 933-1514
E-mail: mashabanemj@gmail.com

18 March 2019

To whom it may concern

Permission to carry out MMED research

This is to confirm that Dr Dinen Parbhoo was granted permission to use renal unit data of Chris Hani Baragwanath Academic hospital for MMED project.

Sincerely

Dr M. J. Mashabane
Head: Division of Nephrology

1.16 Appendix D Data collection sheet

Confidential

Data sheet 1

Study ID _____

Gender
◯ Male
◯ Female

Age _____

Race
◯ African
◯ White
◯ Indian
◯ Coloured
◯ Asian

BMI _____

Cause of ESRD
☐ Diabetes Mellitus
☐ Hypertension
☐ Glomerular Nephritis
☐ PCKD
☐ HIV
☐ Unknown
☐ Other

Other _____

Co-morbid conditions
☐ Dyslipidaemia
☐ Diabetes Mellitus
☐ Hypertension
☐ Thyroid disease
☐ HIV
☐ Other

Other _____

Type of dialysis
◯ Haemodialysis
◯ Peritoneal Dialysis

Change in type of dialysis
◯ None
◯ PD to HD
◯ HD to PD

Year of initiation of RRT _____

ECG
◯ Yes
◯ No

ECG
◯ Acceptable
◯ Not acceptable

ECHO
◯ Yes
◯ No

ECHO
◯ Acceptable
◯ Not acceptable

G-Scope
◯ Yes
◯ No

G-scope
◯ Acceptable
◯ Not acceptable

VCU
◯ Yes
◯ No

VCU
◯ Acceptable
◯ Not acceptable

Carotid doppler
◯ Yes
◯ No

Carotid doppler
◯ Acceptable
◯ Not acceptable

EST
◯ Yes
◯ No

EST
◯ Acceptable
◯ Not acceptable

Abdo ultrasound
◯ Yes
◯ No

Abdo ultrasound
◯ Acceptable
◯ Not acceptable

Blood group
◯ A
◯ B
◯ O
◯ AB

Rh
◯ Positive
◯ Negative

HLA
◯ Done
◯ Not done

PRA's Class I
◯ Positive
◯ Negative

Class I percentage
_____

PRA's Class II
◯ Positive
◯ Negative

Class II percentage
_____

Papsmear
◯ Yes
◯ No

Papsmear
◯ Acceptable
◯ Not acceptable

Angiogram
◯ Yes
◯ No

Angiogram
◯ Acceptable
◯ Not acceptable

RVD
◯ Positive
◯ Negative

On ART
◯ Yes
◯ No

CD4
_____

Viral Load	_____
Hepatitis B	◯ Positive ◯ Negative ◯ Unknown
Hepatitis C	◯ Positive ◯ Negative ◯ Unknown
Current Haemoglobin	_____
Qualifies for transplant	◯ Yes ◯ No ◯ Workup incomplete
Presented	◯ Yes ◯ No
On the list	◯ Yes ◯ No
Suspended	◯ Yes ◯ No
Top 50	◯ Yes ◯ No
Donor Type	☐ Cadaver ☐ RLD
Other Info	_____

1.17 Appendix E Frequency of blood tests suggested by South African Renal Society

Laboratory tests protocol for patients on chronic dialysis

	Per Annum	Jan or Entry	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Haemoglobin*	12	x	x	x	x	x	x	x	x	x	x	x	x
White Cell Count only	4	x			x			x			x		
Platelets	4	x						x			x		
Iron	4	x			x			x			x		
Ferritin	4	x			x			x			x		
Transferrin Saturation	4	x			x			x			x		
Sodium	3	x				x				x			
Potassium	6	x		x		x		x		x		x	
Bicarbonate (CO2 or HCO3)	6	x		x		x		x		x		x	
Urea Pre/Post Dialysis#	12	x	x	x	x	x	x	x	x	x	x	x	x
Creatinine	3	x				x				x			
Parathyroid Hormone (PTH)**	3	x				x				x			
Vitamin D Level	1	x											
Alkaline Phosphatase	1	x											
Calcium Total Corrected (with Albumin)***	6	x		x		x		x		x		x	
Phosphate***	6	x		x		x		x		x		x	
Glucose Random	2	x						x					
HbA1C (Diabetic patients only)	2 (Diabetics only)	x						x					
Lipogram Fasting	1	x											
Total Cholesterol only	1							x					
Hepatitis B S-Antigen	2	x						x					
Hepatitis B E-Antigen****	1	x											
Hepatitis B S-Antibody (if >10, repeat once a year)	2	x						x					
Hepatitis B C-Antibody****	1	x											
Hepatitis C Antibody	2	x						x					
Hepatitis C PCR (only if Hep C Ab positive)	1 (Hep C pos only)	x											
ALT	1	x											
Gamma GT	1	x											
HIV ELISA (with informed consent only)	2	x						x					
CD4 (positive patients only)	3 (HIV pos only)	x				x				x			
Viral Load (positive patients only)	3 (HIV pos only)	x				x				x			

***Repeat Hb:**
Shortly after blood transfusion or hospital admission / As often as weekly if <8.0 / Monthly if <9.0 or >12.5

****PTH level - additional protocol should apply:**
PTH levels above x10 normal range - repeat monthly together with calcium and phosphate levels

*****Post-parathyroidectomy repeat calcium tests:**
Twice per week if <2.0 / Weekly for the first 4 weeks / Monthly for the first 3 months

******Only for patients with Hepatitis B S-antibodies <5 level**

#Can reduce test frequency when online clearance monitoring is used

1.18 Appendix F Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr D Parbhoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M160906

NAME: (Principal Investigator)	Dr D Parbhoo
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	The use of chronic dialysis in a resource-poor environment
DATE CONSIDERED:	30/09/2016
DECISION:	Approved unconditionally
CONDITIONS:	Title change - Certificate re-issued on 1 March 2018
SUPERVISOR:	Dr M Variava
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/10/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

1.19 Appendix G Turnitin report

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