GRAFT SURVIVAL IN SOUTH AFRICAN RENAL TRANSPLANT PATIENTS DURING THE TRANSITION PERIOD AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

(GRAFT-SAT Study)

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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 Master of Medicine in the Department of Paediatrics and Child Health.

Johannesburg 2020

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DECLARATION

I, Priya Darshani Chhiba, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature: 

Date: 26th Day of June 2020

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Thank you to both the Paediatric and Adult Nephrology Clinics at Charlotte Maxeke Johannesburg Academic Hospital. Thank you to the clerks, nurses, and doctors for welcoming me into your units and for assisting me with locating patient records.

Thank you to my family for your support and understanding, especially to my husband for motivating me so much.

Last, but not least; thank you to our wonderful patients and their families whom we serve. I hope that we will always strive to do our best to provide the highest level of quality service to you.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

1. Chhiba PD, Levy C, Moore DP and Do Vale C. Graft survival in South African adolescent renal transplant patients during the transition period at the Charlotte Maxeke Johannesburg Academic Hospital (GRAFT-SAT study). Annual Paediatrics Research Day. 8 November 2019. (Oral Presentation)

ABSTRACT

***Introduction*:** In the developed world, studies performed on the transition of adolescent renal transplant patients have noted high rates of rejection, non-adherence and graft loss. However, there is paucity of data in developing countries, and none in a South African setting.

***Objectives*:** The purpose of this study was to assess the rates of acute and chronic rejection, graft and patient survival in adolescents at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

***Methods*:** This study was a retrospective analysis of patients who received a renal transplant from 1 January 1990 to 31 December 2010, in the Paediatric Nephrology Department at CMJAH, in Parktown, Johannesburg, and entered the adolescent period (10 to 19 years old) with a functioning graft. Patients were included whether or not they were transferred to the Adult Nephrology Department at CMJAH.

***Results*:** 162 recipients were patients were transplanted during the study period, of which 80 (49.4%) were of black race, 63 (38.9%) were white, 10 (6.2%) were Asian and 9 (5.5%) were of mixed race. 65 (40.1%) were female and 97 (59.9%) were male. The median age at transplant was 13.8 years old (Interquartile range (IQR): 10.6 to 15.9). One hundred, twenty-eight (79.0%) patients received a renal transplant during the adolescent period and 34 (21.0%) were transplanted prior to adolescence. Fifty-four (33.3%) patients were transferred to the adult unit during adolescence. Graft failure occurred in 60 (37.0%) of the patients during the adolescent period, of which 54 (90.0%) occurred in the paediatric unit and 6 (10.0%) occurred in the adult unit. The median age at graft failure in the adolescent period was 16.1 years old (IQR: 14.5 to 17.9). Kaplan-Meier curves were used to analyse graft and patient survival. The following factors were identified as statistically significant in contributing to graft failure: if the transplant occurred during adolescence, previous renal transplant,

non-compliance and rejection episodes in the adult unit, (p value <0.05). The 1, 3, 5, and 10-year patient survival rates were 98.8%, 97.6%, 95.1% and 93.9% respectively.

***Conclusion*:** This study revealed high rates of graft rejection and loss in South African renal transplant recipients in the adolescent period highlighting the vulnerability of this population group. Consideration should be given to the creation of transition clinics to potentially improve the graft outcomes of this vulnerable group. Further studies are needed on the transition period of adolescent renal transplant patients.

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LIST OF ABBREVIATIONS

A/C/P	Immunosuppressive regimen 1 – azathioprine, cyclosporine, prednisone
AIC	Akaike information criterion
AKI	Acute Kidney Injury
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
APOL1	Apolipoprotein L1
APSGN	Acute poststreptococcal glomerulonephritis
ARPKD	Autosomal recessive polycystic kidney disease
C/M/P	Immunosuppressive regimen 3 – cyclosporine, MMF, prednisone
CAKUT	Congenital abnormalities of the kidney and urinary tract
CKD	Chronic kidney disease
CL	Confidence limits
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNI	Calcineurin inhibitor
CPG	Clinical practice guideline
DD	Deceased donor
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease

FSGS	Focal segmental glomerulosclerosis
FSH	Focal segmental hyalinosis
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HUS	Haemolytic uraemic syndrome
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
KZN	KwaZulu-Natal
marp	million of the age-related population
MMF	Mycophenolate mofetil
MPGN	Membranoproliferative glomeronephritis
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NHLS	National Health Laboratory Service
NS	Nephrotic syndrome
ODF	Organ Donor Foundation of South Africa
OPD	Outpatients Department
QOL	Quality Of Life
PMP	Per million population
PUV	Posterior urethral valves
Ref.	Reference group

RLD	Related living donor
RPGN	Rapidly progressive glomerulonephritis
RRT	Renal replacement therapy
SARR	South African Renal Registry
SD	Standard deviation
SES	Socio-economic status
T/M/P	Immunosuppressive regimen 2 – tacrolimus, MMF, prednisone
UK	United Kingdom
UKRR	United Kingdom Renal Registry
USRDS	United States Renal Data System
VUR	Vesico-ureteric reflux
WHO	World Health Organisation

1 INTRODUCTION

1.1 BACKGROUND AND HISTORY

Chronic Kidney Disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline (CPG) as "abnormalities of kidney structure or function, present for more than three months, with implications for health" (1). CKD is a clinical syndrome in which there is gradual loss of kidney function over time, with implications on patient health and dependence on care (1). CKD is a global public health problem with the rise in incidence and prevalence of kidney failure resulting in higher costs and poorer outcomes (2).

CKD stems from a wide range of renal insults resulting from various congenital and acquired kidney disorders (1). The rate of progression of CKD is determined by numerous factors including age, underlying aetiology and clinical findings (3). CKD affects various organ systems, therefore children with this disease face lifelong increases in morbidity, mortality and decreased quality of life (QOL) (4, 5). Children with CKD are immunocompromised resulting in increased rates of hospitalisation compared to healthy children (5). Furthermore, CKD impacts on growth, leading to severe growth failure, which may be associated with poor self-esteem (6, 7).

The psychosocial impact of CKD extends beyond the child to its family (6). In addition, children with CKD confront challenges associated with chronic disease, including fatigue, the demands of ongoing medical treatment and recurrent hospital visits (8). These challenges limit school participation and other social activities, and may reduce employment opportunities in their adult years (8).

In the last 20 years, there has been an improvement in the clinical and therapeutic management of childhood CKD, with associated increases in survival and lower complication rate (6). Consequently, there has been a global increase in the number of adult patients dealing with problems unique to childhood-onset CKD (6). CKD in the paediatric population is poorly described with limited information pertaining to the epidemiology of CKD and to its natural course in children and adolescents. However often it progresses to end stage renal disease (ESRD), which is the most serious outcome of CKD (1, 9).

1.1.1 Classification and Staging of Chronic Kidney Disease

The stages of CKD are defined based on the level of kidney function which is defined by the level of the glomerular filtration rate (GFR). This assists the clinician with prognosticating, evaluating and managing a patient with CKD (2). The KDIGO 2012 CPG staging system for CKD in children is tabulated below (Table 1.1) (1).

Table 1.1: Stages of CKD for children based on the KDIGO 2012 clinical practice guideline

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

The GFR is the sum of the filtration rates in all of the functioning nephrons. A reduction of which signifies a decrease in the number of functioning nephrons due to underlying injury or damage (10).

GFR is the most thorough way of indicating renal function as well as renal disease progression (11). It is time consuming and costly to accurately determine GFR, and when applied to the paediatric population, it is also difficult to do so regularly in the clinical setting (11). This has led to the development of formulas which take into account endogenous markers, such as serum creatinine, for the estimation of GFR (11). Creatinine production is a function of muscle mass and is related to a person's body size (10). Normal levels of GFR vary with age, gender and body size (10). A study done by Schwartz et al (12) showed that an estimate of GFR in children can be made from taking a single measurement of the serum creatinine level and body length. This led to the development of the Schwartz formula in the 1970s, which is still widely used in Paediatric Renal Units worldwide (11). The Schwartz formula is:

$$eGFR = \frac{k \times height\ (cm)}{serum\ creatinine} \quad (12)$$

where the constant, *k*, is directly proportionate to the muscle component of the body (12). It varies with the age of the child, and in adolescents it varies with the sex (12). The use of these formulas, which provide an estimated GFR (eGFR), are useful as they can provide data on the GFR at all visits thus allowing the clinician to describe the trend in a patient's GFR over time (11).

Once the eGFR declines to less than 30mL/min/1.73m^2 (Stage G4 CKD) (Table 1.1), patients and their families should be prepared for renal replacement therapy (RRT) (1). Preparation includes counselling the family about haemodialysis, peritoneal dialysis and kidney transplantation (2). Symptoms of ESRD result from deterioration in kidney function and when severe, RRT, in the form of dialysis or kidney transplant, becomes necessary (1). This is the case in 1% of people with CKD, and results in major costs to the health system as well as decreasing the life expectancy of affected patients (1, 13).

1.1.2 End stage renal disease (ESRD)

Progression of CKD with severely reduced GFR (stage G4) to ESRD (stage G5) indicates a sentinel transition point, as stage G5 is considered to be irreversible and requires the initiation of RRT (14). Although ESRD is uncommon in children and adolescents, it is an important health problem in this age group with a reported incidence that varies globally and ranges between 11.9-74.7 cases per year per million of the age-related population (marp) (9, 15-17).

Children and adolescents with ESRD are forced to deal with numerous psychological issues which occur as a result of the chronicity of the disease (8). These include, impaired body image, the feeling of being different from healthy children, and the emotional stress of having to contend with their uncertain futures (8). These factors affect the management of children and adolescents with ESRD (8).

A study done by McDonald et al (18, 19), showed that there has been a significant increase in the long-term survival of children with ESRD in the last 40 years since the introduction of RRT, particularly renal transplantation. Similar findings have been described in studies conducted in Australia, New Zealand and the United States (16, 20). Children who cannot access renal transplantation and are dependent on dialysis, have a higher mortality rate compared to those who have been transplanted (21).

1.2 EPIDEMIOLOGY

1.2.1 Epidemiology of CKD and ESRD

According to the KDIGO guideline, CKD is identified by the presence of kidney damage, either structural or functional, or by the decline in the GFR below 60mL/min/1.73m^2 of body surface area for more than 3 months (1). The epidemiology of CKD is difficult to define as renal dysfunction is a continuum and not an isolated change in renal function, which is applicable to both children and adults (6). Worldwide data on the epidemiology of CKD in the paediatric population is scanty and likely underdiagnosed due to earlier stages of CKD being largely asymptomatic, resulting in an underestimation of the incidence and prevalence of the disease in this particular group (6, 15). This is compounded in resource-limited countries due to the inadequacy of health care facilities making it difficult to compare the rates of childhood CKD globally, both in terms of the care of children with CKD as well as collecting accurate population based data (15). In the majority of studies, estimates of CKD in paediatrics arise from patients with moderate to severe CKD or those already in ESRD (6). The available data on childhood CKD is usually published from major referral centres and it is not known if this information truly reflects population-based risks (15). Furthermore the burden of CKD in children in developing countries, including sub-Saharan Africa is unknown and difficult to estimate because of the lack of available data, in particular the notable absence of renal registries (22).

To change the course of progression of CKD to ESRD, earlier identification of CKD needs to occur, with symptoms and signs of earlier stages of disease progression being identified (9). However, childhood CKD registries are restricted, scarce and limited to only small reference populations (6, 9). The lack of population-based data results in registries being created on the basis of RRT data, even though most children only reach this stage when they are beyond the paediatric age group, which leads to under-representation of the paediatric population in existing databases (9, 23).

A prospective population-based registry, The ItalKid Project, was created in Italy in 1990 (9). In the first 10 years of the registry, 1197 patients were registered (9). The mean incidence of CKD during the last 5 years was 12.1 (Range, 8.8 to 13.9) cases per year per million of the age-related population (marp) (9). The prevalence of paediatric CKD in the subsequent year, was 74.7 per marp (9). In comparison, the estimated mean incidence of paediatric stage 3 to 5 CKD in Europe is 11.9 cases per marp and 8.0 per marp for CKD stages 4-5 (15). A similar burden of CKD and ESRD has been reported in other population-based registries from Western countries (20). In contrast, the incidence of CKD (not staged) in paediatric studies in Latin America, ranged from 2.8 to 15.8 cases per marp (15). In the Middle East and South East Asia, the mean incidence of CKD was 38.0 per marp with an increase in prevalence from 188.0 per marp in 1996 to 329.0 per marp in 2003 (17). Factors suggested to contribute to this high prevalence include cultural, social and religious beliefs as well as the absence of a specialised paediatric transplant service (17) (Table 1.2).

There is a large knowledge gap regarding the epidemiology of CKD in African adult and paediatric populations, as there are no national data systems in place to enable the collection, analysis and reporting of patients with CKD (24). Reports of incidence and prevalence of CKD from Africa are largely from single centre studies (15). The burden of CKD in children and its incidence, prevalence and outcome on the South African health care system is largely unknown (24). A study done by Bhimma et al (24) in 2007 in KwaZulu-Natal (KZN) revealed an annual incidence of CKD in children of 1.0 to 2.0 per marp. A Nigerian study had the same annual incidence rate of CKD in children of 1.0 to 2.0 per marp (25) (Table 1.2).

ESRD is uncommon in children and the incidence and prevalence in the paediatric population varies throughout the world (15). New Zealand reported the highest estimated rate of ESRD in children, with an annual rate of 18 per million children (15). According to the United States Renal Data System

(USRDS), the incidence of ESRD in children and adolescents in the United States is decreasing from a high 17.5 per million population (PMP) in 2004, to 15.0 PMP in 2013 (25). The United Kingdom (UK) Renal Registry (UKRR) reported an incidence rate of treated ESRD in children of 9.4 per marp and a prevalence rate of 60.4 per marp 2014 (26). In contrast, a lower annual incidence of ESRD was reported in Japan, with a rate of 4.0 per million children (15). Paediatric ESRD incidence varies across Europe, ranging from 3.6 to 8.1 per million children annually (15). The USRDS annual report shows a 21.7% decrease in the number of children and adolescents requiring ESRD care, from 17.5 per million population in 2004 to 13.7 per million population in 2015 (25) (Table 1.2).

As previously mentioned, there is a paucity of data for CKD and ESRD in the paediatric population in sub-Saharan Africa (27). Children with ESRD in sub-Saharan Africa may have the poorest outcomes globally due to a combination of factors including poor socio-economic conditions, late presentation, absence of medical insurance and inadequate health infrastructure (27). ESRD incidence was increased compared to previous years in the Nigerian study, which was attributed to a possible increase in recognition and referral of children in ESRD (27). Poor health seeking behaviour, underreporting of cases and referral patterns in poor resource settings may be the reason for the lower incidence of ESRD in the paediatric population in Nigeria when compared to developed countries (27). In the study, it was thought that the differences in the referral patterns were due to increased awareness, recognition and referral of children with ESRD in communities which were closer to the University College Hospital (27). A study done in Cameroon revealed an ESRD incidence in children of 1.7 per marp, lower than reported in developed countries (28). (See Table 1.2 comparing the above incidence rates).

Table 1.2: Table showing the incidence of CKD and ESRD in various countries

Country (reference)	Year	CKD incidence (Cases per marp)[1]	ESRD incidence (Cases per marp)[1]
United Kingdom and Europe			
United Kingdom (26)	2014	10.2	9.4
Italy (15)	1990 – 2000	12.1 (8.8 – 13.9)	-
Belgium (29)	2001 – 2005	11.9	-
Spain (30)	2007 – 2008	8.7	-
France (31)	1975 – 1990	10.5	-
North America			
United States of America (USA) (25)	2004	-	17.5
	2013	-	15.0
South America			
Latin America (15, 32)	1989 – 1996	2.8 – 15.8	-
Argentina			
Brazil			6.5
Colombia			-
Mexico			
Uruguay			
Chile (15, 32)	1996	5.7	
Asia			
Middle East, South East Asia(29)	1996	38.0	-
Jordan (29)	1996	11.0	-
Vietnam (33)	1996	5.0	5.0
Japan (15)	2014	-	4.3
Bangladesh, Nepal (15)	1995 – 2002	-	<1.0
Oceania			
New Zealand (15)	1996	-	8.0
Australia (15)	1996	-	8.0
Africa			
South Africa (Kwa-Zulu Natal [KZN]), SA (34)	2007	1.0 – 2.0	-
South West Nigeria (34)	1985 – 2000	3.0	3.6
	2009-2012	-	4.4
Cameroon (22)	2015	-	1.7

[1]Cases per marp – per million of the age-related population.

1.2.2 Epidemiology of RRT

According to the USRDS report, children with ESRD were more likely to be initiated onto haemodialysis compared to peritoneal dialysis or renal transplantation (25). In 2015, 51.9% of children were initiated onto haemodialysis, compared to 26.6% and 21.3% for peritoneal dialysis and renal transplantation respectively (25). During the period 2010 through 2015, 36.0% of children with ESRD received a transplant in their first year of ESRD care, and in 2015 the rate of renal transplantation was 33.6 per 100 dialysis patients per year (25). Since 2009 there has been a decline in the number of related living donor transplants in the United States, with living donor transplants accounting for only 38.6% of renal transplants in 2015 (11.9% decrease since 2009) (25). Over the 15 years, from 2001 to 2015, 1715 children and adolescents had received RRT in the UK, according to the UKRR (26). In the UK increasing age was associated with an increase in the prevalence of RRT, and RRT was more frequent in males (26).

1.2.3 Sex, Race and Age

The incidence and prevalence of CKD is greater in males compared to females, because of the higher frequency of congenital abnormalities of the kidney and urinary tract (CAKUT) in males (15). This is supported by the UKRR (26) as well as the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry which showed an unbalanced sex distribution in the youngest age groups with 70.0% of 0-1 year and 66.0% of 2-5 year old patients being male (20). The distribution however evened out in adolescence, where 56.0% of the patients were male (20).

Race is another factor which affects the epidemiology of CKD (15). Data from registries in North America (the NAPRTCS), the Australia and New Zealand Dialysis and Transplant Registry (AZNDATA) and the UKRR, all reported an increased risk for CKD in ethnic minority group populations (20, 26, 35). Alluding to the potential role of high-risk genotypes resulting in a faster

decline in renal function over time (36). The NAPRTCS registry from North America revealed that the burden of CKD is two to three times higher in African-American children compared to Caucasian children (20). In the African-American population, the genotype of apolipoprotein L1 (APOL1) may explain the increased risk for CKD (36). This high-risk genotype is associated with an increased risk for developing glomerular disease as well as a faster decline in renal function over time compared to children with low-risk genotypes (36). In Australia and New Zealand, children with indigenous ethnicity are at an increased risk for both acute kidney injury (AKI) and CKD (35). The rates of ESRD in those of indigenous ethnicity, compared to Caucasian children, are similar in children under the age of 14 years old, but increase after 15 years of age (35). A study done in KZN, South Africa found that the incidence of glomerulonephritis was higher in black children compared to other racial groups, which was in keeping with reports from developed countries (24, 37). The reasons behind this racial bias were unknown in the study although a genetic basis was proposed (24).

1.2.4 Socio-Economic Factors

The increasing burden of ESRD places a strain on resources in all countries, with emerging economies being disproportionately affected (38). There is marked disparity in the management of paediatric ESRD patients when comparing developed and developing countries (21). The vast majority of treated ESRD patients reside in more developed countries, which can afford the cost of RRT, which in turn influences the outcome of these children (21). The average annual cost of RRT per patient far exceeds the gross domestic income per capita of most developing countries (38) and there is a high mortality rate reported in countries with poorer economies and inadequate healthcare resources for RRT (21). In a tertiary centre in India, up to 40.0% of ESRD patients stopped further RRT because of financial constraints (39).

The constraints on capital and human resources affecting developing countries forces clinicians to ration RRT (38). A few developing countries able to afford RRT programmes, such as South Africa, regulate this scarce resource in the public health sector, resulting in many patients being declined dialysis (38, 40). Rationing of expensive medical resources has become a reality in most developing countries (38). In Western Cape centres, patients with ESRD are usually screened based on medical and socioeconomic criteria and the decision of the outcome is then taken by an Assessment Committee (38). A South African study by Moosa et al (38), showed that patients most likely to be accepted for RRT were those who were aged 20-40 years old, white, employed, married, non-diabetic and those living in close proximity to a dialysis centre. Furthermore, 60.0% of patients were denied RRT because of social factors relating to poverty, with these factors influencing the decision for RRT more than the medical factors did (38). Thus, patients in South Africa, which is recognised as a middle-income country, have limited access to RRT.

Other factors which lead to limited access to renal services include lack of financial resources, lack of human resources, rural location of population, lack of government will, the burden of HIV/AIDS in sub-Saharan Africa, lack of basic amenities (sanitation, running water and electricity), inaccessibility/lack of cheap transport, late diagnosis of CKD and poor nutrition (38). It is well known that minority groups have less chance of accessing treatment or interventions, including RRT (38). In the study by Moosa et al (38), patients were selected for RRT based on psychosocial and medical factors, with psychosocial factors influencing decision making more than medical factors. In that study, the most significant criterion determining which patients qualified for RRT was whether the patient was suitable for renal transplantation according to Assessment Committee report (38). The next most important criterion was access to treatment facilities (38). The process of rationing RRT was noted to be severely flawed, despite its good intentions, resulting in an inequality of service delivery with the poor being the most disadvantaged (38).

Van Biljon et al (40) reviewed the first report on the paediatric data of the South African Renal Registry (SARR). In 2012, 59 children had received RRT in South Africa, with the RRT prevalence rate of 3.8 per marp, much lower than that of developed countries (40). Global RRT prevalence rates in developed countries are between 20.0 to 80.0 per marp for children aged 0-14 years (40).

In countries where RRT is readily available, renal transplantation is the treatment modality of choice in children with ESRD (21). In North America, 16.0% of newly diagnosed patients with ESRD received a pre-emptive renal transplant and 75.0% of children on dialysis will receive a renal transplant within three years of initiating dialysis; these figures correlate with the ANZDATA registry (19, 25).

The care of children with ESRD imposes a burden on an already burdened health care budget in developing countries (41). Furthermore, poor socioeconomic conditions in parts of the world mean that children with ESRD may not receive adequate treatment, especially those requiring RRT (41). In Nigeria, the management of paediatric patients with ESRD was reported to be challenging because of a late presentation of patients, as well as a number of poor socioeconomic factors including the absence of medical insurance, inadequate health infrastructure and poor government support (27).

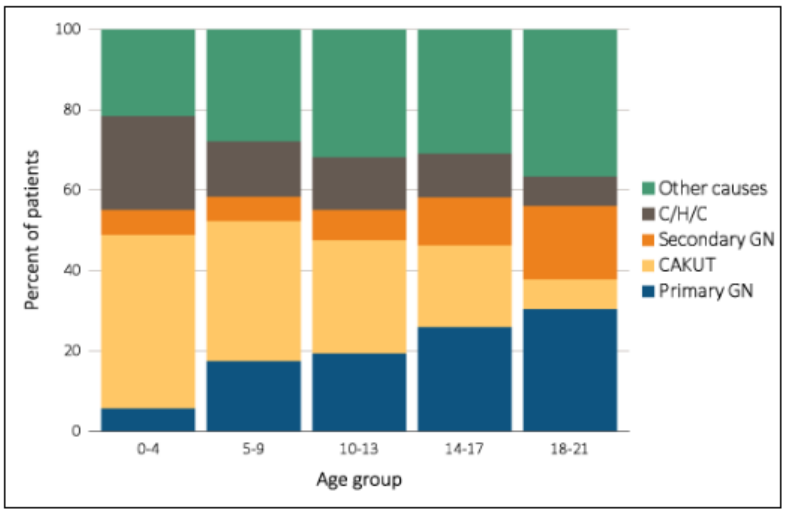
1.3 AETIOLOGY

The common primary renal diseases which lead to ESRD in adults include diabetic nephropathy, hypertension and autosomal dominant polycystic kidney disease (42). These diseases rarely cause ESRD in children (42). Congenital and primary inherited disorders, (e.g. renal dysplasia) and obstructive uropathies are the common primary causes of ESRD in young children (42). In contrast; acquired glomerular diseases, such as focal segmental glomerulosclerosis (FSGS) and lupus nephritis are more likely to cause ESRD in older children (7).

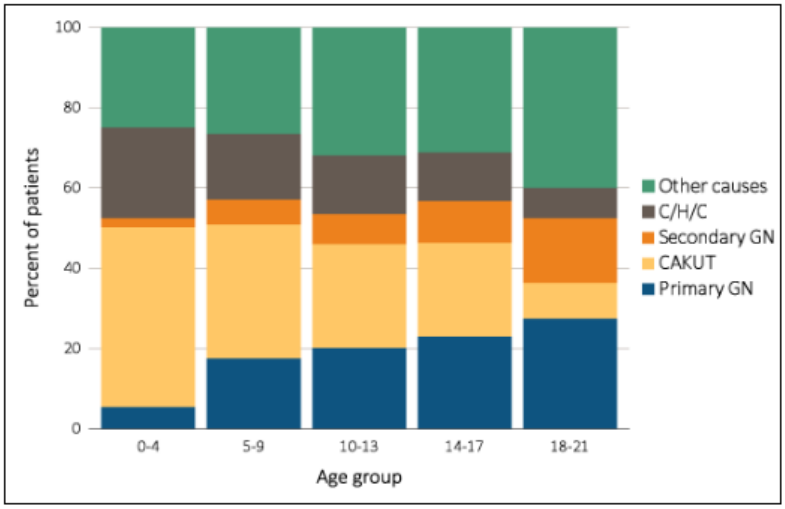
According to the USRDS, the common causes of ESRD in children during 2011-2015 was CAKUT, accounting for 22.0% of cases, followed by primary glomerular disease (21.8%) (25). 12.5% of cases were accounted for by cystic/hereditary/congenital disorders and 10.7% were secondary glomerular disease/vasculitis (25). The most common individual diagnoses of paediatric ESRD included FSGS (11.6%), renal hypoplasia/dysplasia (10.0%), congenital obstructive uropathies (9.7%) and systemic lupus erythematosus (SLE) (6.3%) (25); Figure 1.1.

The aetiology of ESRD in developing countries is similar regardless of geographic setting (24). In India, South Africa and Nigeria, glomerulonephritis (including nephrotic syndrome) was the leading underlying diagnosis associated with CKD in 26.0% to 69.0% of cases (34, 39, 43, 44). In a study by Bhimma et al (24) from KZN, a rise in the incidence of FSGS was noted. Haemolytic uraemic syndrome (HUS) was infrequently diagnosed in children, and was seen in 5.4% of children under 5 years of age and in 7.0% of older children with CKD (24). The authors speculated that the higher prevalence of glomerulonephritis in their study population may have been due to the higher referral rate of this group of patients to a tertiary institution because of obvious symptoms, including impetigo, oedema, and dyspnoea on presentation (24). The study also reported a high prevalence (43.7%) of

stage 2-5 CKD in children under 5 years, which was higher than that reported from centres in other developing countries (24).



(a) 2006 – 2010



(b) 2011 – 2015

Figure 1.1: Distribution of reported incident paediatric ESRD patients by primary cause of ESRD, by age in (a) 2006 – 2010 and (b) 2011 – 2015. This figure is from the USRDS website and reproduced with permission obtained from the USRDS (25).

Data Source: Special analyses, USRDS ESRD Database.

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; C/H/C, Cystic/Hereditary/Congenital diseases; GN, glomerulonephritis

1.4 ADOLESCENTS AND ESRD

The World Health Organisation (WHO) defines adolescence as "the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19 years, which represents one of the critical transitions in the life span" (45). Adolescence and young adulthood is known to be a confusing and tumultuous time of life, regardless of physical health (46). With the transition into adulthood, adolescents and young adult patients move out of their comfortable, familiar paediatric environment into unknown and often much busier adult units, where they are expected to become more independent and take on increased responsibility for their own health (46, 47).

There is a high risk of non-adherence in the adolescent age group for numerous reasons and they may be ill equipped to assume responsibility for their own health and medical condition (46). Previously accepted medical advice and guidance may be turned down, with an increased tendency to reject authority (48). The physical changes which are associated with puberty, along with the natural tendency to explore and push boundaries, have a profound impact on the social and emotional functioning of adolescents (48). Adolescents tend to become more conscious of their body image, and frequently depend on their peers for approval and guidance (48). Medical illness may impact greatly on many adolescents, making them feel different or imperfect in comparison to their peers (48).

An important component of adolescent development is that they are more impulsive and prone to participating in risky behaviours (48). Adolescents tend to feel as though they are invincible and immune to their impulsivity (48, 49). Teenagers are unable to fully understand the long term outcomes of their lifestyle choices which includes experimentation with the use of alcohol and recreational substances, unprotected sexual activities and unsafe and thoughtless behaviours (48). The majority of adolescents with ESRD have dealt with chronic illness from a very early period in their lives and

they are unable to remember what it is to feel “normal” (50). Many children with chronic diseases may have had delayed onset of puberty and they may have witnessed other, healthy adolescents engaging in risky behaviours (50).

Entering adolescence and young adulthood puts children with chronic diseases at risk of unsafe behaviours, including engaging in sexual activity (50). Adolescents, including renal transplant patients carry the highest burden of sexually transmitted infections (STI’s) (50). In a study conducted by Ashoor and Pasternak (50), there was a 30.0% STI prevalence in a review of adolescent renal transplant patients older than 13 years over a 5-year period. According to the WHO, 16 million girls aged 15-19 years and 1 million girls under 15 years old give birth annually in low to middle income countries (51).

Worldwide in 2012, there were about 2.1 million adolescents living with HIV (52). Statistics have also shown that of all new HIV infections, approximately 14.0% occur during the adolescent period (52). Adolescents in particular are vulnerable to HIV infection, especially when living in areas with a high burden of HIV, or if they belong to groups who are at increased risk for acquiring or transmitting HIV infection through sexual transmission (52). In a study of South African adolescents, 37.5% in the 15-24 year group had more than one sexual partner compared to 18.3% in the 25-49 year old age group (53). In the 15 to 24 year old age group, the incidence of HIV was 7.1% while in the 0-14 year age group, the HIV incidence was 2.4% in 2012 (53).

1.5 RENAL TRANSPLANTATION AND TRANSITION CLINICS

In patients with ESRD, the treatment of choice is renal transplantation (54). Several studies have shown improved life expectancy with renal transplantation compared to dialysis (55). A study from Australia and New Zealand showed that renal transplant decreased the risk of death 4-fold compared to dialysis (18). Renal transplantation has led to an improvement in the survival of children with ESRD, as well as an improved quality of life (56).

In the USA, approximately 800 renal transplants are performed annually in children under 18 years of age (57). According to the NAPRTCS Registry, more males than females are transplanted due to the higher number of male patients with CAKUT that progresses to ESRD (20). In South Africa, the Organ Donor Foundation (ODF) reported a total of 249 renal transplants in 2016, of which, 234 (94.0%) were in adults, 12 (4.8%) in children and 3 (1.2%) in adolescents (58). In the paediatric and adolescent group, 6 (40.0%) of the renal transplants were from live related donors (58). In South Africa it is difficult to put children with ESRD onto RRT programmes because of various factors, which include the high cost of RRT, lack of trained staff, late referral of patients with CKD to tertiary level institutions and the poor socio-economic status of patients (24).

There has been an increase in patient and renal graft survival due to improvements in the care of young patients and in the immunosuppressive regimens used post renal transplantation, which has resulted in a reduction of the frequency and severity of acute rejection (18). The improvement of graft survival over time, irrespective of whether the graft was from a deceased donor (DD) or a related living donor (RLD), has been attributed to multiple factors, including; improved pre-transplantation preparation, enhanced surgical techniques, better donor choices, more potent immunosuppressive medications and use of evidence-based protocols (7). Children aged 5 years or younger have shown

the most dramatic improvement following renal transplantation amongst all age groups, including adults (7). However, with transplantation comes complex polypharmacy regimens, ongoing monitoring, and strict fluid and diet restrictions. Therefore, the success of the renal transplant is dependent on compliance with immunosuppressive treatment (8, 59).

Significant risk factors for graft survival include older recipient age, poor socio-economic status (SES), black race, diabetes, delayed graft function and the presence of rejection in the first year (60). Racial disparities in acute rejection and graft survival have been documented in both paediatric and adult renal transplant patients (61). Several factors, including immunological factors, variability in absorption and effect of immunosuppressive medications, differing underlying disease spectrums and hypertension may play a role in contributing to lower graft survival in black patients (61).

Adolescents have been shown to have the worst long-term graft survival amongst all paediatric-recipient age groups (7). Studies have previously shown that adolescent and young adult transplant patients have the highest rates of acute and chronic rejection, following poor adherence, compared to the general transplant recipient population (62). There are numerous factors associated with increased non-adherence; including low SES, family instability, risk-taking behaviour and poor understanding of the importance of adherence to treatment (46). The risk of non-adherence is further increased in adolescents or young adults who have not been sufficiently prepared for the transition into adult orientated health care systems (46). A study by Watson et al (59) found a 35.0% allograft loss in patients in the first 3 years post-transfer of patients to adult care if a transition clinic was not in place. Studies have shown, that there is increased non-adherence in patients of lower SES (46).

A small number of studies from high income countries have shown the feasibility of establishing transition clinics to bridge the void between paediatric- and adult-centred care, resulting in improved graft survival in adolescent renal transplant patients (63). Transition clinics may serve as a stepping stone from paediatric to adult nephrology clinics whereby adolescents are assessed for their readiness for transfer, as well as providing support and encouragement to the patient and to their families (56). Transition clinics can provide education to patients and to their families which would include information on immunosuppressive regimens, emphasis on adherence and consequences of non-adherence (56). Sexual behaviours, as well as recreational drug and alcohol use, are issues addressed at transition clinics (56) as unsafe sexual behaviour results in an increase in unplanned pregnancies and new HIV infections, complicating the management of these patients (50).

Prestidge et al (62) compared patient and allograft survival in renal transplant patients who received care from a transition clinic, versus those who were transferred directly to the adult nephrology unit. Patients transferred directly to adult care experienced significantly worse outcomes (9.0% died and 21.0% experienced allograft rejection) compared to those that attended a transition clinic (which had no deaths nor allograft losses) (62). In addition those transitioned into adult care had an improved and significant difference in 2-year graft and patient survival (62).

On reviewing the available literature, only one article from a developing country (India) examined the outcomes of adolescent renal transplant patients during their transition period to adult care (64). Srivastava et al (64) compared the adolescent outcomes of living donor transplant in the developing world to the developed world (high income countries). They found early graft survival to be comparable, however the 5-year graft survival was markedly inferior at 66.8% in the developing world compared to 85.7% in the developed world (64). The authors attributed reduced allograft survival to non-adherence with immunosuppressive regimens due to socio-economic constraints (64).

Currently there is no literature available examining the outcomes of adolescent renal transplant patients within the South African setting.

1.6 AIMS

To assess renal graft survival and specific secondary health outcomes in children, who received a renal transplant and entered the transition period (ten to nineteen years of age), at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), paediatric and adult renal clinics.

1.7 OBJECTIVES

1.7.1 Primary:

1. To describe the graft survival in adolescents (10 to 19 years of age) during the transition period.
2. To document the number of rejection episodes during the transition period.

1.7.2 Secondary:

1. To document the rate of decline in graft function during the transition period.
2. To determine patient survival up to five years post transfer from paediatric to adult renal clinics.
3. To document the following secondary outcomes in our cohort:
    a) HIV infection
    b) Pregnancy

2 METHODS

2.1 STUDY DESIGN

This study was a retrospective analysis of paediatric patients who received a renal transplant and entered the transition period (ten to nineteen years of age) over a 20-year period, from 1 January 1990 to 31 December 2010, in the Paediatric Nephrology Department at CMJAH whether or not they were transferred to adult Nephrology department at CMJAH. Analysis of the data for this study was carried out by analysing the two main components, both separately and in certain instances as a comparison, namely patient characteristics and graft characteristics.

2.2 STUDY SETTING

The study was conducted at CMJAH, in Parktown, Johannesburg. Data was collected, with permission, from the Paediatric Nephrology Department as well as the Transplant Unit of the Division of Adult Nephrology, Department of Internal Medicine. In the paediatric nephrology unit, on average, about 137 patients, are seen per month, of which about 130 are old patients. There are about 6 to 10 post-renal transplant patients seen per month (personal communication, Dr Glenda Moonsamy, Head Paediatric Nephrology, CMJAH). The paediatric clinic is serviced by 5 doctors, ranging from paediatric nephrologists (n=3), a registrar and medical officer rotating through nephrology. With respect to the spectrum of illness seen in the paediatric clinic; the top 4 diagnoses, in descending order of frequency are: nephrotic syndrome, CAKUT (other), PUV, and other diagnoses. On average, approximately 40 renal transplant patients are seen in the adult clinic per week (personal communication, Dr Claudia Do Vale, Internal Medicine, Department of Nephrology, CMJAH). There are between 10 to 12 doctors, ranging from adult nephrologists (n=4), registrars (n=4), and medical officers (n=3).

2.3 STUDY POPULATION

2.3.1 Inclusion Criteria

- All patients who received a functional allograft between 1st January 1990 and 31st December 2010 and entered adolescence (ten years of age) with a functioning graft.

2.3.2 Exclusion Criteria

- Patients transplanted before 1 January 1990 or after 31st December 2010, whether or not they entered adolescence.
- Patients with graft failure prior to adolescence (10 years of age)
- Patients who demised prior to adolescence (10 years of age)
- Patients transplanted after adolescence (turned 19 years old)

2.4 DATA COLLECTION

Patients for the study were identified by using the Transplant Registry in the department of Paediatrics. Cases included those patients who had received a renal transplant during 1990 through 2010. Study subjects who met the above criteria, were allocated a random study identity number, to ensure that all data was captured anonymously. Data capturing were done on site and patient records were kept on hospital premises at all times. Password protected software was used for data capturing and storage. No patient identifiers were entered onto the study database.

Once the study subjects were identified, their hospital records were retrieved. The data collected from the Paediatric Nephrology Department included the following:

- Demographic characteristics:
    - Age- at transplant and on transfer to adults
    - Sex
    - Race
    - Hospital financial classification
- Transplant details:
    - Date of transplant
    - Type of transplant [RLD or DD]
    - If RLD: the donor's relationship to the patient (parent, sibling or other)
    - The number of transplants received
    - Immunosuppressive regimens
- Rejection episodes: dates, number and type
- Renal transplant biopsy results

Financial classification data were obtained from administration offices at the hospital. Data were extracted by the primary investigator onto a data collection sheet prior to entry into the electronic database.

Serum creatinine levels and eGFR done at the following time points were recorded and analysed to determine changes in graft function.

- At the time of transplant
- Two months following transplant
- One-year post transplant, and then annually up until 10 years after receiving the transplant

- Before transition
- At 21 years of age or death or graft failure

Hospital records of those patients transferred to the Adult Transplant Unit were also used to record serum creatinine levels and eGFR up to and including 5 years after transfer to adults from the Paediatric Nephrology Department. Some of the data (serum creatinine levels) which were not found in the patient's hospital files, were then obtained using the DISA system at NHLS on CMJAH premises. Other data was found in the hospital's medical records department located on the fourth floor at CMJAH.

2.4.1 Financial Classification and Socio-economic Status

The financial classification system at CMJAH was used to analyse the financial classification of the patients. Patients classified as H0 are those on social pension, government grants (disability or social). H1 are individuals with an income less than R36 000.00 per annum and households with an income less than R50 000.00 per annum. H2 are individuals with an income less than R72 000.00 per annum and households with an income less than R100 000.00 per annum. H3 are individuals with an income greater than or equal to R72 000.00 per annum and households with an income greater than or equal to R100 000.00 per annum. PF are foreign patients without documentation. PH are patients who are on a medical aid, prisoner, suspect or road accident victims.

For the purpose of this study, in terms of analyses conducted and reporting, the SES of the patients was combined into five SES groups: low, middle, private, foreign, and unknown. The low SES group was made up of the H0 group, and the middle SES group comprised H1, H2, H3 CMJAH financial categories. PH fell under the private group, and PF was under the foreign group. The unknown group included those patients in which the financial classification could not be found (either missing data from the files or inadequate notes).

2.4.2 Categorisation of Aetiologic Diagnoses

Aetiologic diagnoses precipitating CKD were classified into three groups: 'glomerular disease', 'congenital', and 'other'. Diagnoses included in the 'glomerular disease' group consisted of acute post-streptococcal glomerulonephritis (APSGN), focal segmental glomerulosclerosis (FSGS), focal segmental hyalinosis (FSH), glomerulonephritis (GN) and rapidly progressive glomerulonephritis (RPGN). 'Congenital' aetiologies of CKD included autosomal recessive polycystic kidney disease (ARPKD), congenital nephrotic syndrome, dysplastic kidneys, posterior urethral valves (PUV), primary reflux nephropathy, and vesico-ureteric reflux (VUR). Diagnoses not included in the glomerulonephritis or congenital categories were assigned to the 'other' category.

2.4.3 Secondary Objectives

2.4.3.1 HIV Infection

Doctor's notes in the patient files were reviewed for the diagnosis of HIV. The NHLS laboratory system was also used to obtain information regarding HIV infection when there was no documentation in the patients' files.

2.4.3.2 Pregnancy

The files of the female patients in the cohort were reviewed for information regarding whether the patient fell pregnancy. The NHLS laboratory system was also used to obtain information regarding beta HCG serum tests, when there was no documentation in the patients' files.

2.5 LIST OF DEFINITIONS

1. **Acute rejection**: "Defined using clinical and biochemical data. This included an elevation of serum creatinine more than 15% above the baseline, a reduction in urine output and a response to rejection therapy" (65).
2. **Adolescence**: "The period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19 years, which represents one of the critical transitions in the life span" (45).
3. **Akaike information criterion (AIC)**: This is an estimator of the relative quality of the statistical models for a given set of data, it provides a means for the selection of various models (66).
4. **Allograft failure**: "Progressive decline in renal function during the course of at least 3 months in the absence of another cause, for example, recurrent glomerulonephritis, renal artery stenosis or obstruction" (65).
5. **Ethnicity**: "Defined as stated by the patient/family, it is reported as White, Black, Mixed race, Asian, Indian or Other" (26).
6. **Graft failure**: The need for the recipient to either be initiated onto dialysis, to return onto dialysis or to require another renal transplant (60).
7. **Graft survival**: The need for the recipient to either be initiated onto dialysis, to return onto dialysis, or to require another renal transplant" (60).
8. **Non-compliance**: was defined as patients who had missed appointments during the study period.
9. **Rejection episode**: "Defined by a physician's decision to initiate specific antirejection therapy" (20). It is also deemed to have occurred if rejection is the reported cause of graft failure, even in the absence of an acute rejection report (20). In this study, rejection episodes were identified by the increase in serum creatinine, following which the patient was treated with anti-rejection therapy. Rejection episodes were analysed based on when in the study

period they had occurred – if they had occurred during the adolescent period, in the paediatric or the adult unit, or if they had occurred prior to the patient entering the adolescent period in the paediatric unit. The number of rejection episodes were also documented, if they had occurred during the adolescent period, either in the paediatric or in the adult unit.

10. **Renal Replacement Therapy (RRT)**: "All patients with renal transplants and patients who are receiving haemodialysis or peritoneal dialysis" (26).
11. **Transition period**: A period between stages of life in human development, adolescence is the transition period between two stable states of development, namely childhood and adulthood (67).

2.5.1 Approach to Analysis of Patient Transfer to the Adult Renal Service

Data from the patient dataset, rather than the graft dataset were used to analyse the number of patients transferred to the adult nephrology unit. The reason for using this dataset, is that even though some of the patients received more than one renal transplant in the paediatric nephrology unit, they were transferred across to the adult team with their last transplant received in the paediatric unit. Furthermore, the analysis took into account whether the patient was transferred to the adult unit during the adolescent period or out of the adolescent period.

2.6 STATISTICAL ANALYSIS

STATA software was used for analysis of the descriptive statistics, which were reported as medians and interquartile ranges (IQR) for the continuous variables. Frequencies and percentages were used for categorical variables. Graft failure was analysed separately for the patient and the graft datasets. Analysis took into account when the graft failure occurred, whether it was in or out of the adolescent period, as well as in which department it occurred – either the paediatric or the adult nephrology units. Data from the last clinic visit were used in the patients who were lost to follow up. The creatinine value taken at last follow-up was used to establish whether the graft was function or failing at time of last follow-up or time of patient censoring.

Patient survival was defined as the time from transplant to death, and was censored at date of last follow-up, transfer to another facility, or loss to follow-up. The patient survival model was constructed using descriptive and inferential statistics. The following parameters were used in the patient survival model:

1. Whether death occurred in or out of the adolescent period;
2. The date of death;
3. Demographic variables: sex, race, financial classification, diagnosis group;
4. Transplant characteristics: renal transplant occurred in the adolescent period or not, the type of renal transplant (RLD or DD), immunosuppressive regimen used, and the total number of transplants received by the patient in the study period;
5. The decade during which the transplant occurred (1990's or 2000's);
6. The baseline eGFR measurement;
7. The date of the last eGFR measurement, as well as the final eGFR measurement.

Graft survival was defined as the time between the date of transplant, and the date of graft failure. Grafts that were not known to fail, either because the patient was lost to follow, transferred to another facility, or still had a functioning graft at the last observed date, or the patient demised, were censored. The date of censoring was considered as the date of lost to follow up, transfer to another facility, last eGFR obtained at age 19 years, or the date of death. The graft survival model was constructed using descriptive and inferential statistics. The following parameters were used in the model:

1. Date of renal transplant;
2. Date of graft failure during the adolescent period;
3. Graft failure occurred during the adolescent period;
4. Date of lost to follow up;
5. Date of last eGFR at 19 years old;
6. Date of death.

Kaplan-Meier curves and log-rank tests were used to describe and compare the patient and graft survival rates in univariate analyses. The chi-square method was used to test for significance, and a p-value of <0.05 was considered to be statistically significant. Variables analysed in univariate patient and graft survival analyses included: demographic factors (sex, race, SES, renal diagnosis), transplant characteristics (transplant during the adolescent period, decade in which the transplant occurred, immunosuppressive regimen, type of graft (RLD or DD), and the total number of grafts received by the patient during the study period), eGFR values (taken at the time of the renal transplant [baseline eGFR], and the final eGFR taken at the time of graft failure [final eGFR]), transfer to the adult unit during the adolescent period, compliance to immunosuppressive medications, and rejection episodes prior to, and during the adolescent period. Survival analysis models were analysed for both the patient and graft data, interrogating patient and graft survival. Censored data was taken into account for the survival analyses.

Cox proportional hazards regression modelling were used to construct the multivariate analysis for variables associated with patient and graft survival. Models were adjusted for potentially confounding variables that could have influenced the patient and graft outcomes. Models which gave rise to the lowest Akaike information criterion (AIC) were maintained for reporting in the patient and graft survival results.

R version 3.6.1 (68) was used for the survival analyses, using the survival (69, 70), survminer (71), and survivalAnalysis (72) packages.

2.7 ETHICS APPROVAL

Ethics approval for the conduction of this retrospective study was obtained from the University of the Witwatersrand Human Research Ethics Committed (Medical), clearance certificate number M160405. In the initial ethics submission, age, creatinine values and heights were only collected as specified in the original protocol. These were at the following time periods:

- At transplant;
- At 2 months;
- One year after transplant;
- Before transfer to the Adult Nephrology Department;
- At 21 years of age;
- At death;
- At graft failure.

Approval was obtained from the University ethics department for an amendment to the data collection, this would be to ensure complete data collection. These additional values were at the same periods as those collected in the adult nephrology unit (as per the original protocol and ethics approval). There was no change to the risks to the patients (this was a retrospective study). The following additional time periods were applied for, and approved by the Ethics committee:

- Two years following renal transplant;
- Three years following renal transplant;
- Four years following renal transplant;
- Five years following renal transplant;
- Six years following renal transplant;
- Seven years following renal transplant;
- Ten years following renal transplant.

3 RESULTS

3.1 OVERVIEW

A total of 188 patients underwent 255 renal transplants in the 20-year period, between 1 January 1990 and 31 December 2010 in the Paediatric Nephrology Department at CMJAH. There was a median of 1 transplant per patient (Range, 1 to 4). There were 26 patients excluded from the patient survival analysis: 14 (53.8%) because of missing data and 12 (46.2%) due to graft failure or death occurring before the adolescent period or because the transplant occurred outside of the adolescent period. Hence, 162 patients were available for analysis (Figure 3.1).

In the graft survival analysis 255 grafts were transplanted in the study period, of those, 42 grafts were not included in the data set. Twenty-five (59.5%) grafts were excluded as graft failure occurred before the adolescent period, or the graft was transplanted after the adolescent period. Of the remaining grafts excluded, 16 (38.1%) were excluded because of missing data or damaged patient records and 1 (2.4%) was excluded as the patient died prior to the adolescent period. Hence, 213 grafts were available for analysis (Figure 3.1).

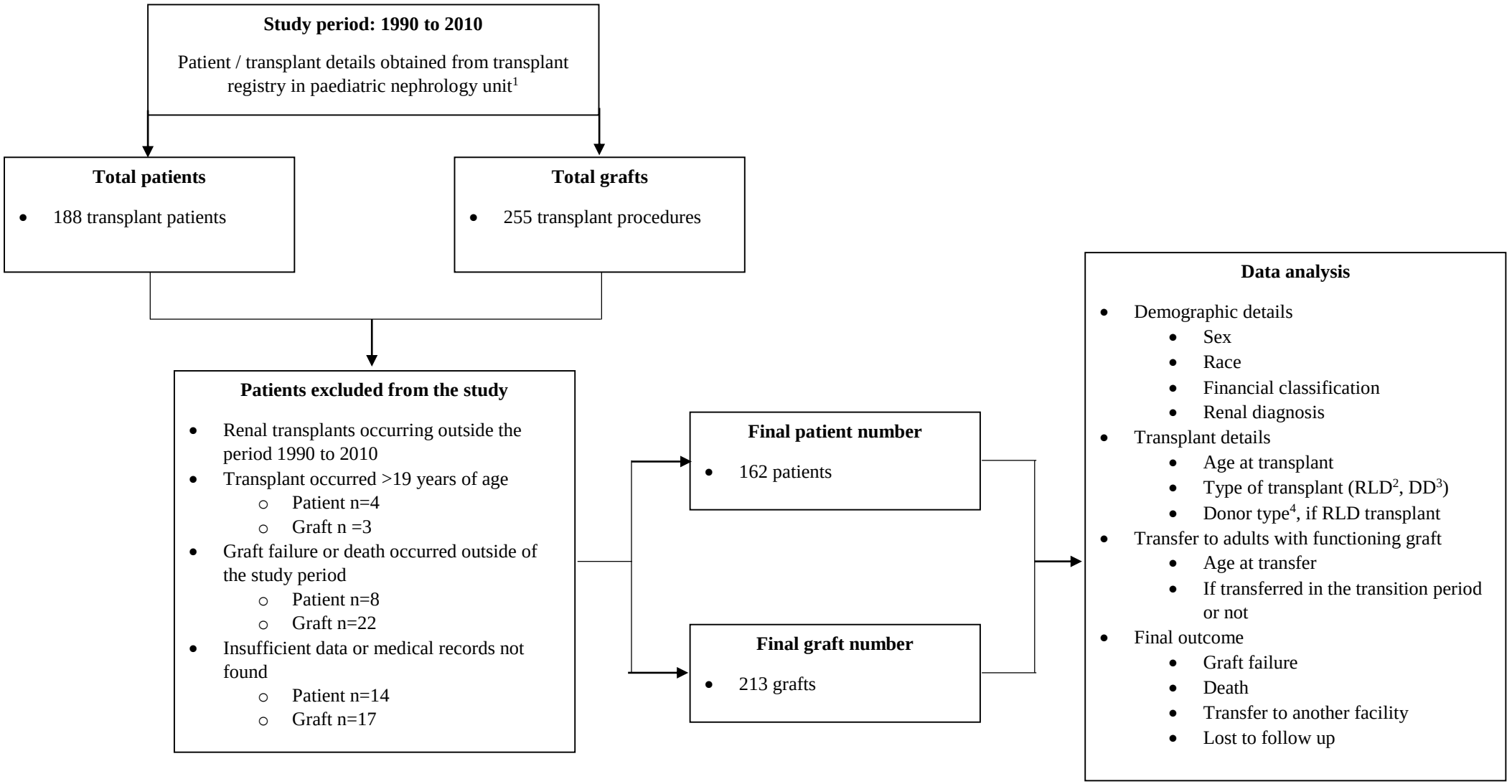


Figure 3.1: Schematic overview of study method

[1] Patient / transplant details obtained from transplant registry in paediatric nephrology unit – transplant registry kept under lock and key in the unit; [2] RLD – related living donor; [3] DD – deceased donor; [4] Donor type – Mother/Father/Sibling/Other (Aunt)

3.2 PATIENT CHARACTERISTICS

3.2.1 Demographics (Gender, Race, Age, SES)

Of the 162 patients, 65 (40.1%) were female and 97 (59.9%) male. Eighty (49.4%) patients were black, 63 (38.9%) were white, 10 (6.2%) were Asian and 9 (5.5%) were of mixed race. Ten (6.2%) of the 162 patients were classified as belonging to the low SES group. The majority (n=89; 54.9%) of the patients fell within the middle SES. Thirty-nine (24.1%) patients were in the private group, and there was 1 (0.6%) foreign patient. Twenty-three (14.2%) patients had unknown SES (Figure 3.2, and Table 3.1).

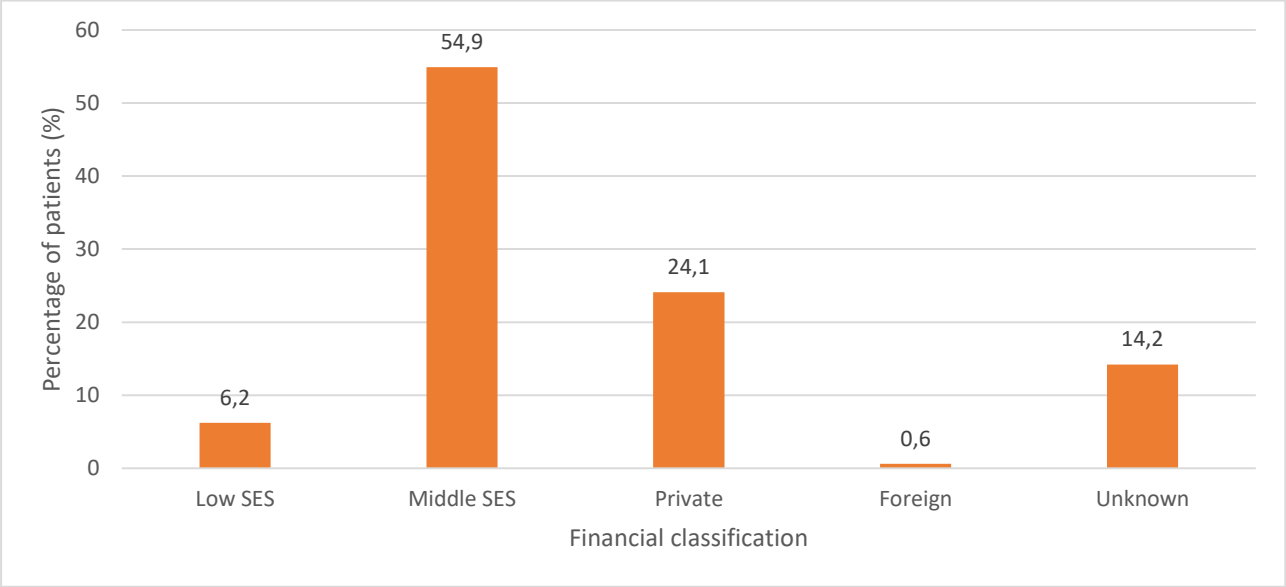


Figure 3.2: Frequency of each *financial classification* for patient data

Overall, the median age of the patients transplanted was 13.8 years (IQR: 10.6 to 15.9). One hundred, twenty-eight (79.0%) patients received a renal transplant during the adolescent period (10 to 19 years old) (Table 3.2).

3.2.2 Aetiology of CKD

The ‘top 10’ diagnoses associated with aetiology of chronic kidney disease included dysplastic kidneys (n=26; 16.1%), PUV (n=21; 13.0%), FSGS (n=19; 11.7%), congenital nephrotic syndrome (n=14; 8.6%), primary reflux nephropathy (n=14; 8.6%), FSH (n=11; 6.8%), RPGN (n=11; 6.8%), ARPKD (n=10; 6.2%), HUS (n=7; 4.3%) and VUR (n=6; 3.7%). The ‘top 10’ diagnoses accounted for 85.8% (n=139) of the 162 transplant recipients (Table 3.1).

Of the remaining diagnoses GN, lupus nephritis, and APSGN affected 5 (3.1%), 3 (1.9%) and 1 (0.6%) case respectively. There were 14 (8.6%) other diagnoses including medullary cystic kidney, Takayasu’s arteritis, Lawrence Moon Biedl Syndrome, Henoch Schönlein Purpura (HSP), and primary hyperoxalosis. All 162 patients had a defined aetiology of the underlying CKD (Table 3.1).

Ninety-one patients (56.2%) fell under the congenital group, 47 (29.0%) cases occurred in the glomerular disease group and 24 (14.8%) fell under the other group (Table 3.1).

Table 3.1: Demographic characteristics and aetiology of CKD for the patient dataset

Characteristic	**Patient data N=162**
Sex, n (%)	
Female	65 (40.1)
Male	97 (59.9)
Racial group, n (%)	
Black	80 (49.4)
White	63 (38.9)
Asian	10 (6.2)
Mixed race	9 (5.5)
Financial classification, n (%)	
Low SES [1]	10 (6.2)
Middle SES [2]	89 (54.9)
Private [3]	39 (24.1)
Foreign [4]	1 (0.6)
Unknown [5]	23 (14.2)
Diagnosis (individual), n (%)	
Dysplastic kidneys	26 (16.1)
PUV [6]	21 (13.0)
FSGS [7]	19 (11.7)
Congenital nephrotic syndrome	14 (8.6)
Primary reflux nephropathy	14 (8.6)
Other [8]	14 (8.6)
FSH [9]	11 (6.8)
RPGN [10]	11 (6.8)
ARPKD [11]	10 (6.2)
HUS [12]	7 (4.3)
VUR [13]	6 (3.7)
Glomerulonephritis	5 (3.1)
Lupus nephritis	3 (1.9)
APSGN [14]	1 (0.6)
Diagnosis (combined), n (%)	
Glomerular disease group [15]	47 (29.0)
Congenital group [16]	91 (56.2)
Other group [17]	24 (14.8)

[1] Low SES – patients on social pension, government grants (disability or social); [2] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [3] Private – patients on a medical aid, prisoner, suspect or road accident victims; [4] Foreign – foreign patients without documentation (illegally in South Africa); [5] Unknown – patients of unknown SES; [6] PUV – posterior urethral valves; [7] FSGS – focal segmental glomerulosclerosis; [8] Other - medullary cystic kidneys, Takayasu's arteritis, Lawrence Moon Biedl Syndrome, Henoch Schönlein Purpura, and primary hyperoxalosis; [9] FSH – focal segmental hyalinosis; [10] RPGN – rapidly progressive glomerulonephritis; [11] ARPKD – autosomal recessive polycystic kidney disease; [12] HUS – haemolytic uraemic syndrome; [13] VUR – vesico-ureteric reflux; [14] APSGN – acute post-streptococcal glomerulonephritis; [15] Glomerular disease group – consisting of APSGN, FSGS, FSH, GN and RPGN; [16] Congenital disease group – ARPKD, congenital nephrotic syndrome, dysplastic kidneys, PUV, primary reflux nephropathy, and VUR; [17] Other – HUS, SLE, medullary cystic, Takayasu's arteritis, Lawrence Moon Biedl Syndrome, HSP, and primary hyperoxalosis.

3.2.3 Allograft details

One hundred, and nine (67.3%) patients received one renal transplant, 32 (19.7%) received two transplants, 17 (10.5%) received three renal transplants and 4 (2.5%) received four renal transplants in total. The median ages of patients that received one, two, three or four renal transplants were 13.3 years (IQR: 9.4 to 14.9), 15.0 years (IQR: 13.2 to 16.5), 14.8 years (IQR: 13.1 to 16.2), and 16.9 years (IQR: 15.8 to 17.6) respectively. Overall, the median age at transplant was 13.8 years (IQR: 10.6 to 15.9). One hundred, twenty-eight (79.0%) patients received a renal transplant during the adolescent period (10 to 19 years old); Table 3.2.

Seventy-six (46.9%) of the transplants occurred prior to the year 2000. Of the patients who received one graft overall, 47 (43.1%) occurred during the 1990's, and 62 (56.9%) were during the 2000's. In contrast, of the group that received four renal transplants, 3 (75.0%) were during the 1990's, and 1 (25.0%) was during the 2000's; Table 3.2.

The majority of patients (n=101; 62.3%) had DD renal transplants; however, of the 109 patients who received one transplant 57 (52.3%) had RLD grafts. Four patients received four renal transplants in the study period. Only one of the four (25.0%) received a graft from an RLD for one of the renal transplants and the rest received all of their grafts from a DD (Table 3.2 and Figure 3.3).

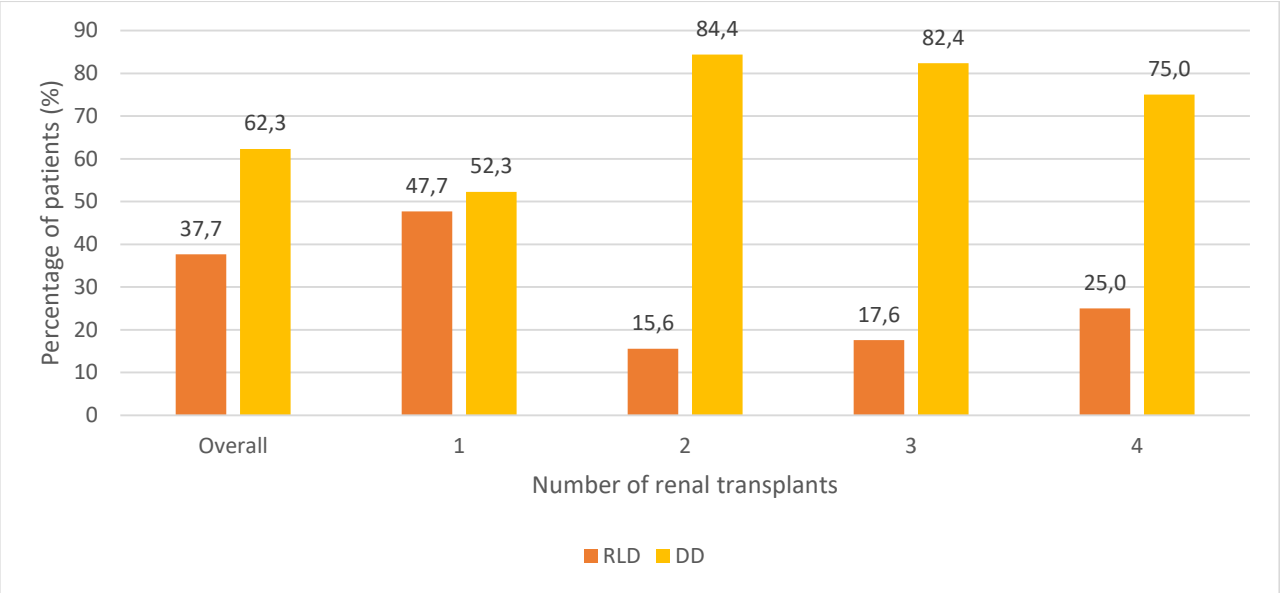


Figure 3.3: Distribution of the *type of transplant* received for each renal transplant in the study period

Overall, 34 (55.7%) RLD transplants were from the patients' mothers, 20 (32.8%) were from their fathers, 4 (6.6%) were from siblings and 1 (1.6%) from an aunt. In 2 (3.3%) cases, the relatedness of the RLD donor to the patient were unknown. In the group that received one renal transplant, the patient's mother accounted for 29 (55.8%) of the grafts, followed by the patient's father (n=19; 36.5%), siblings (n=3; 5.8%) and an aunt (n=1; 1.9%) (Table 3.2).

Three immunosuppressive regimens were utilised during the 20-year study period:

- Regimen 1: Azathioprine, cyclosporine and prednisone
- Regimen 2: Tacrolimus, mycophenolate mofetil (MMF) and prednisone
- Regimen 3: Cyclosporine, MMF and prednisone

In 2000, the paediatric nephrology unit at CMJAH changed from Regimen 1 to Regimen 2.

Overall there were 82 (50.6%) patients on Regimen 1, 68 (42.0%) on Regimen 2 and 12 (7.4%) on Regimen 3. For the first renal transplant 48 (44.0%) patients were on Regimen 1, 56 (51.4%) were on Regimen 2, and 5 (4.6%) were on Regimen 3. Most of the patients who received a second or third transplant in the study period (n=49) were on Regimen 1 (32; 65.3%), while 10 (20.4%) received Regimen 2 and 7 (14.3%) received Regimen 3. Two (50.0%) patients that received four transplants were on Regimen 1 and the other two patients were on Regimen 2; Figure 3.4 and Table 3.2.

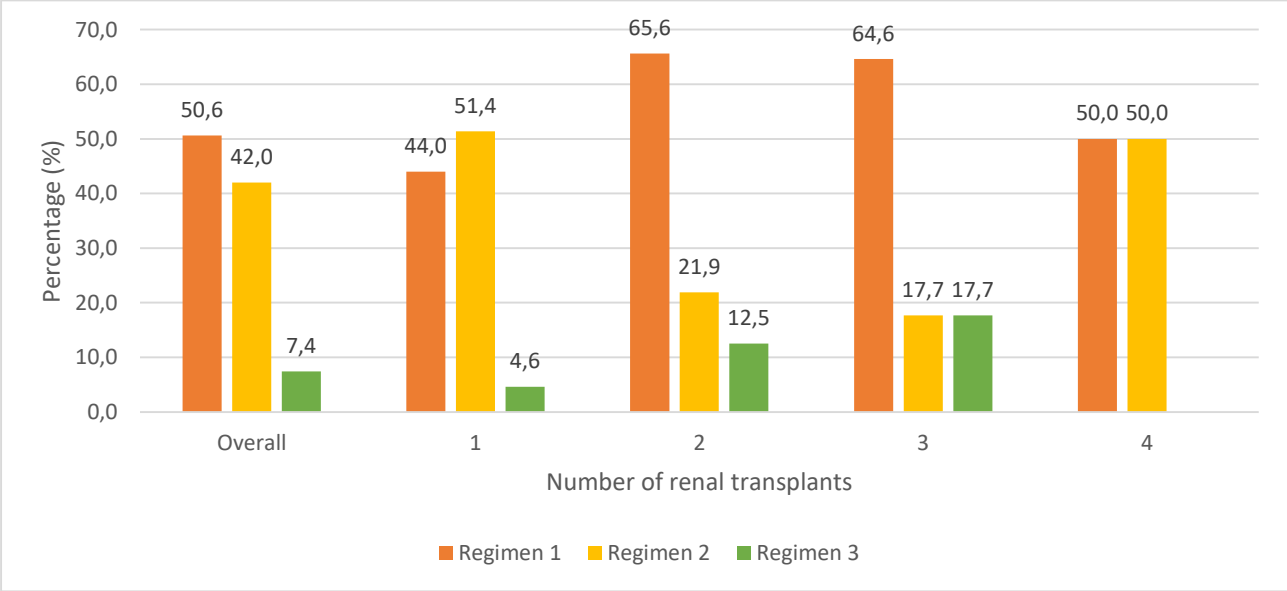


Figure 3.4: Immunosuppressive regimen *per number of renal transplants*

During the 1990's Regimen 1 was used in 71 (93.4%) of patients, while Regimen 2 and Regimen 3 were used in 2 (2.6%) and 3 (4.0%) of patients respectively. Regimen 2 was the most frequently used regimen used in the 2000's, accounting for 66 (76.7%) of the cases, followed by Regimen 1 in 11 (12.8%) cases, and Regimen 3 in 9 (10.5%) cases; Table 3.2.

Table 3.2: Transplant details for patient dataset in the study period

Variable	Overall [1] N=162	Number of patients that received a renal transplant during the study period [2]			
		One [3]	Two [4]	Three [5]	Four [6]
Patients, n (%)	162	109 (67.3)	32 (19.7)	17 (10.5)	4 (2.5)
Age (years), median (IQR)	13.8 (10.6, 15.9)	13.3 (9.4, 14.9)	15.0 (13.2, 16.5)	14.8 (13.1, 16.2)	16.9 (15.8, 17.6)
Decade transplanted, n (%)	162	N=109	N=32	N=17	N=4
1990's	76 (46.9)	47 (43.1)	18 (56.2)	8 (47.1)	3 (75.0)
2000's	86 (53.1)	62 (56.9)	14 (43.8)	9 (52.9)	1 (25.0)
Type, n (%)					
RLD [7]	61 (37.7)	52 (47.7)	5 (15.6)	3 (17.7)	1 (25.0)
DD [8]	101 (62.3)	57 (52.3)	27 (84.4)	14 (82.3)	3 (75.0)
Donor, if RLD [9], n (%)					
Mother	34 (55.7)	29 (55.8)	3 (60.0)	1 (33.3)	1 (100.0)
Father	20 (32.8)	19 (36.5)	1 (20.0)	0 (0.0)	0 (0.0)
Sibling	4 (6.6)	3 (5.8)	0 (0.0)	1 (33.3)	0 (0.0)
Aunt	1 (1.6)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	2 (3.3)	0 (0.0)	1 (20.0)	1 (33.3)	0 (0.0)
Immunosuppressive regimen, n (%)					
Regimen 1 [10]	82 (50.6)	48 (44.0)	21 (65.6)	11 (64.6)	2 (50.0)
Regimen 2 [11]	68 (42.0)	56 (51.4)	7 (21.9)	3 (17.7)	2 (50.0)
Regimen 3 [12]	12 (7.4)	5 (4.6)	4 (12.5)	3 (17.7)	0 (0.0)

[1] Overall – total number of patients receiving a renal transplant; [2] Total number of renal transplants received by patient – either one, two, three or four renal transplants overall; [3] One – patient had one renal transplant 109/162 records available; [4] Two – patient had two renal transplants 32/162 records available; [5] Three – patient had three renal transplants 17/162 records available; [6] Four – patient had four renal transplants 4/162 records available; [7] RLD – related living donor, 61/61 records available; [8] DD – deceased donor, 101/101 records available; [9] Donor, if RLD – 61/61 records available; [10] Regimen 1 – Azathioprine/cyclosporine/prednisone; [11] Regimen 2 – Tacrolimus/mycophenolate mofetil (MMF)/prednisone; [12] Regimen 3 – Cyclosporine/MMF/prednisone.

3.2.4 Outcomes

3.2.4.1 Transfer to adult nephrology unit

Of the 162 patients, 81 (50.0%) were transferred to the adult nephrology unit with a functioning graft, 54 (66.7%) of whom were transferred during the adolescent period and 27 (33.3%) were transferred out of the adolescent period (aged >19 years); Figure 3.5. The other 81 (50.0%) patients remained in the Paediatric Nephrology Department. Of these patients, 58 (71.6%) had graft failure, 16 (19.8%) were transferred to another facility, 5 (6.2%) demised, and 2 (2.4%) were lost to follow up.

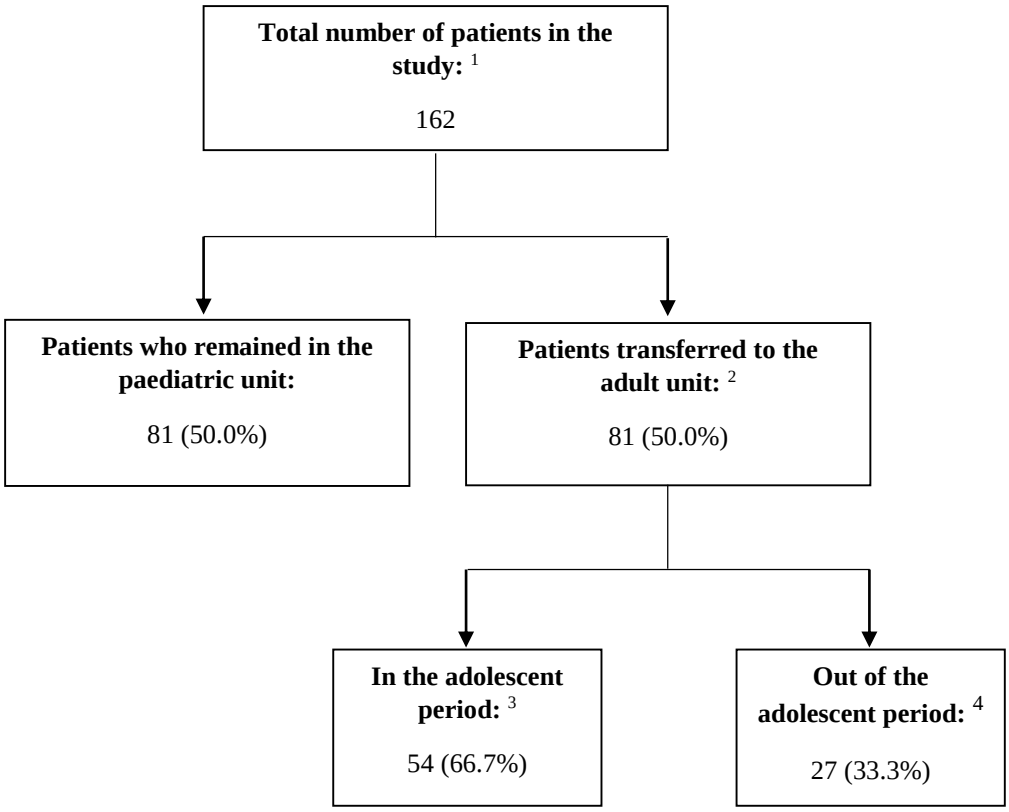


Figure 3.5: Summary of patient transfer to the adult nephrology unit

[1] Total number of patients; [2] Patients transferred to the adult unit – all transferred across with a functioning graft; [3] In the transition period – between the ages of 10 to 19 years old; [4] Out of the transition period – transferred to adults at age >19 years.

Of the 81 patients transferred to adults with a functioning graft, the median age at transfer was 18.4 years (IQR: 17.5 to 19.3). Thirty-one (38.3%) were female and 50 (61.7%) were male. With respect to race, 44 (54.3%) patients transferred to the adult nephrology unit were black, 28 (34.6%) were white, 6 (7.4%) were of mixed race and 3 (3.7%) were Asian. Overall, the majority of the patients transferred to the adult unit fell in the middle SES, accounting for 50 (61.7%) of the patients. Sixty-eight (84.0%) received their renal transplant during the adolescent period and 13 (16.0%) were transplanted before the adolescent period. Forty-seven (58.0%) received grafts from a DD, and 34 (42.0%) had RLD transplants. With respect to the relationship of the donor to the recipient, 19 (55.9%) of the RLD grafts were from mothers, 12 (35.3%) were from fathers, 2 (5.9%) were from siblings, and in 1 (2.9%) case the RLD was unknown; Table 3.3.

Table 3.3: Characteristics of the patients transferred during the adolescent period in the study period

Variable	Overall transferred to adults [1]	Transfer to adult unit N=81		Remained in paediatric nephrology unit
		In adolescent period [2]	Out of adolescent period [3]	
Patients transferred, n (%)	81 (50.0)	54 (66.7)	27 (33.3)	81 (50.0)
Age (years) at transfer, median (IQR)	18.4 (17.5, 19.3)	17.9 (16.6, 18.4)	19.8 (19.3, 21.1)	N/A
Sex, n (%)				
Female	31 (38.3)	25 (46.3)	6 (22.2)	34 (42.0)
Male	50 (61.7)	29 (53.7)	21 (77.8)	47 (58.0)
Race, n (%)				
Black	44 (54.3)	29 (53.7)	15 (55.6)	36 (44.5)
White	28 (34.6)	19 (35.2)	9 (33.3)	35 (43.2)
Asian	3 (3.7)	2 (3.7)	1 (3.7)	7 (8.6)
Mixed race	6 (7.4)	4 (7.4)	2 (7.4)	3 (3.7)
Financial classification, n (%)				
Low SES [4]	7 (8.6)	6 (11.1)	1 (3.7)	3 (3.7)
Middle SES [5]	50 (61.7)	34 (63.0)	16 (59.3)	39 (48.1)
Private [6]	16 (19.8)	10 (18.5)	6 (22.2)	23 (28.4)
Foreign [7]	1 (1.3)	1 (1.9)	0 (0.0)	0 (0.0)
Unknown [8]	7 (8.6)	3 (5.5)	4 (14.8)	16 (19.8)
Transplanted in adolescence, n (%)				
Yes	68 (84.0)	43 (79.6)	25 (92.6)	60 (74.1)
No	13 (16.0)	11 (20.4)	2 (7.4)	21 (25.9)
Type, n (%)				
RLD [9]	34 (42.0)	23 (42.6)	11 (40.7)	27 (33.3)
DD [10]	47 (58.0)	31 (57.4)	16 (59.3)	54 (66.7)
Donor, if RLD [11], n (%)	N=34	N=23	N=11	N=27
Mother	19 (55.9)	11 (47.9)	8 (72.7)	15 (55.6)
Father	12 (35.3)	10 (43.5)	2 (18.2)	8 (29.6)
Sibling	2 (5.9)	1 (4.3)	1 (9.1)	2 (7.4)
Aunt	0 (0.0)	1 (4.3)	0 (0.0)	1 (3.7)
Unknown	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.7)

[1] Overall – total number of patients that were transferred to the adult unit 81/162; [2] In the adolescent period – transferred to adults between ages 10 to 19 years old 54/81; [3] Out of the adolescent period – transferred to adults >19 years old 27/81; [4] Low SES – patients on social pension, government grants (disability or social); [5] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [6] Private – patients on a medical aid, prisoner, suspect or road accident victims; [7] Foreign – foreign patients without documentation (illegally in South Africa); [8] Unknown – patients of unknown SES; [9] RLD – related living donor; [10] DD – deceased donor; [11] Donor, if RLD.

3.2.4.2 Transfer to another facility

Of the 162 patients, 15 (9.3%) were transferred to another facility in the adolescent period, of whom 7 (46.7%) were transferred to another province, 5 (33.3%) to private, 2 (13.3%) overseas, and 1 (6.7%) to another academic institution. Thirteen (86.7%) of the patients transferred to another facility were in the paediatric unit, and 2 (13.3%) patients were in the adult nephrology unit (Figure 3,6).

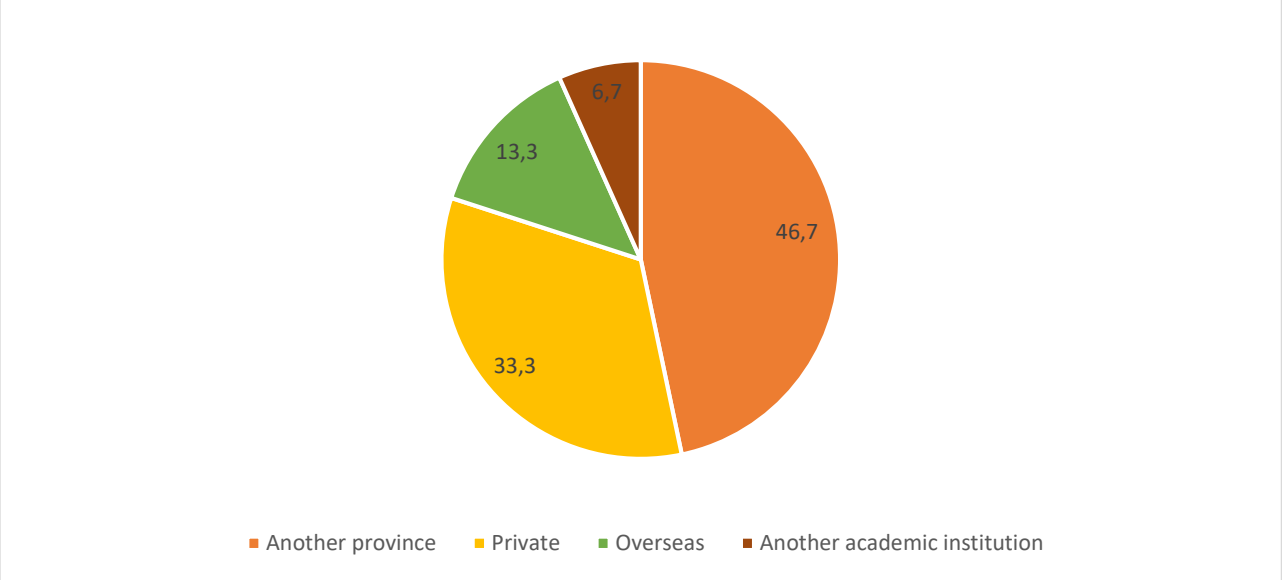


Figure 3.6: Pie chart illustrating the percentage of patients *transferred to another facility*

The median age at transfer to another facility was 16.4 years (IQR: 15.0 to 18.3), and 8 (53.3%) were female. The majority (n=10; 66.7%) of the patients transferred to other facilities were white. None of the patients transferred to another facility were in the low SES group, or the foreign patient group; Table 3.4.

Of the 15 patients transferred to another facility, 5 (33.3%) received a graft from an RLD, of which the mother was the donor in 2 (40.0%) of the cases, and the patient's father was the donor in 3 (60.0%)

of the cases. Ten (66.7%) of the patients received a graft from a DD. The majority (n=9; 60.0%) of patients transferred out to other facilities were on Regimen 1, 5 (33.3%) were on Regimen 2 and 1 (6.7%) patient was on Regimen 3. The majority (n=12; 80.0%) of the patients transferred out to other facilities received one transplant in the study period; Table 3.4.

3.2.4.3 Lost to follow up

Three (1.9%) of the 162 patients were lost to follow up during the adolescent period, 1 (33.3%) from the paediatric unit, and 2 (66.7%) from the adult nephrology unit. The median age at lost to follow up was 17.8 years (IQR: 10.7 to 18.3). Two (66.7%) of those lost to follow up were female, and 2 (66.7%) were black patients; Table 3.4.

All 3 patients that were lost to follow up were transplanted prior to the adolescent period, and all of them received an RLD graft, the donor being the patient's mother in all the cases. Regimen 2 had been used in all 3 patients who were lost to follow up, and all 3 had received one transplant during the study period; Table 3.4.

Table 3.4: Characteristics of patients transferred to another facility and lost to follow up

Variable	Transferred to another facility [1]	Lost to follow up [2]
Patients, n (%)[3]	15 (9.3)	3 (1.8)
Age (years), median (IQR)	16.4 (15.0, 18.3)	17.8 (10.7, 18.3)
Sex, n (%)		
Female	8 (53.3)	2 (66.7)
Male	7 (46.7)	1 (33.3)
Race, n (%)		
Black	1 (6.7)	2 (66.7)
White	10 (66.7)	1 (33.3)
Asian	2 (13.3)	0 (0.0)
Mixed race	2 (13.3)	0 (0.0)
Financial classification, n (%)		
Low SES [3]	0 (0.0)	0 (0.0)
Middle SES [4]	5 (33.3)	2 (66.7)
Private [5]	7 (46.7)	1 (33.3)
Foreign [6]	0 (0.0)	0 (0.0)
Unknown [7]	3 (20.0)	0 (0.0)
Transplanted in adolescence, n (%)		
Yes	10 (66.7)	0 (0.0)
No	5 (33.3)	3 (100.0)
Type, n (%)		
RLD [8]	5 (33.3)	3 (100.0)
DD [9]	10 (66.7)	0 (0.0)
Donor, if RLD [10], n (%)		
Mother	2 (40.0)	3 (100.0)
Father	3 (60.0)	0 (0.0)
Sibling	0 (0.0)	0 (0.0)
Aunt	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Immunosuppressive regimen, n (%)		
Regimen 1 [11]	9 (60.0)	0 (0.0)
Regimen 2 [12]	5 (33.3)	3 (100.0)
Regimen 3 [13]	1 (6.7)	0 (0.0)

[1] Transfer to another facility during the adolescent period; [2] Lost to follow up during the adolescent period; [3] Patients, n (%) – number of patients who were censored (denominator=162); [3] Low SES – patients on social pension, government grants (disability or social); [4] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [5] Private – patients on a medical aid, prisoner, suspect or road accident victims; [6] Foreign – foreign patients without documentation (illegally in South Africa); [7] Unknown – patients of unknown SES; [8] RLD – related living donor; [9] DD – deceased donor; [10] Donor, if RLD; [11]Regimen 1 – Azathioprine/cyclosporine/prednisone; [12]Regimen 2 – Tacrolimus/mycophenolate mofetil (MMF)/prednisone; [13]Regimen 3 – Cyclosporine/MMF/prednisone.

3.2.4.4 Graft failure

Of the 162 patients, graft failure occurred in 98 (60.5%), 59 (60.2%) of which occurred while the patients were following up in the paediatric nephrology unit, and 39 (39.8%) occurred in the adult nephrology unit. Sixty (61.2%) patients experienced graft failure during the adolescent period. Of the 59 patients who experienced graft failure in the paediatric unit, 54 (91.5%) lost the graft during the adolescent period, and 5 (8.5%) lost the graft outside of the adolescent period (graft failure occurred either < 10 years old, or > 19 years old). Of the 39 patients who lost the graft in the adult unit, the majority (n=33; 84.6%) were >19 years of age at the time of graft failure; Figure 3.7. The median age at graft failure in the paediatric unit was 16.1 years (IQR: 14.5 to 18.0), versus 21.1 years old (IQR: 19.6 to 24.2) in the adult unit (p-value<0.001).

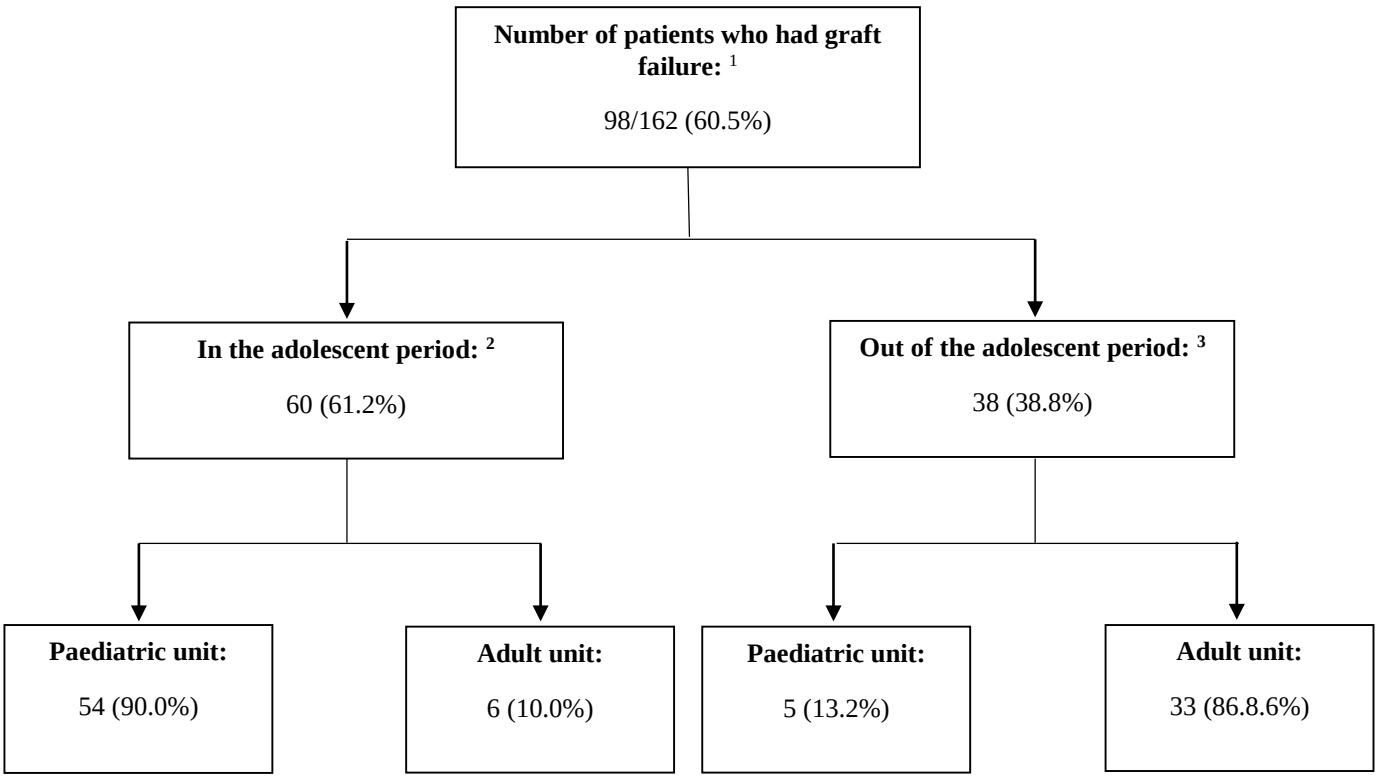


Figure 3.7: Flow diagram summarizing graft failure: Patient Dataset

[1] Total number of patients who had graft failure of the study group. [2] Graft failure – occurred during the adolescent period – both paediatric and adult units. [3] Graft failure – occurred outside of the adolescent period – both paediatric and adult units.

Overall, the median age of the patients with graft failure, in both the paediatric and adult units, was 18.1 years old (IQR: 15.6 to 20.4). The youngest patient was 10.7 years old, and the oldest was 34.2 years. The majority of patients experiencing graft failure (n=61; 62.2%) were male. Graft failure occurred in 58 (59.2%) black patients, 31 (31.6%) white patients, 5 (5.1%) patients of mixed race, and 4 (4.1%) Asian patients. The majority (n=54; 55.1%) of the patients with graft failure were in the middle SES category; Table 3.7.

Of the 54 patients that experienced graft failure during the adolescent period in the paediatric unit, 32 (59.3%) were males. Four (66.7%) of the 6 patients with graft failure during the adolescent period and receiving treatment in the adult unit were male. There were 31 (57.4%) black patients who lost their graft in the paediatric unit, 19 (35.2%) white patients, 3 (5.5%) Asian patients, and 1 (1.9%) patient of mixed race. The median age of patients who had graft failure within the adolescent period in both the paediatric and adult units combined, was 16.1 years old (IQR: 14.5 to 17.9). The youngest patient was 10.7 years old, and the oldest was 18.8 years old. All 6 patients who had graft failure during the adolescent period in the adult unit, were of black race. The majority of the patients experiencing graft failure in both the paediatric and adult units, fell under the middle SES group for the financial classification, accounting for 30 (55.6%) and 4 (66.7%) of patients respectively; Table 3.5.

The most frequent overall cause of graft failure during the adolescent period was rejection (n=22; 36.7%), followed by non-compliance (n=21; 35.0%). Primary non-function, chronic allograft nephropathy and recurrence of primary disease precipitated graft failure during the adolescent period in 8 (13.3%), 6 (10.0%), and 3 (5.0%), respectively; Table 3.5.

Rejection was the most frequent cause of graft failure (n=21; 38.9%) in patients with graft failure during adolescence treated in the paediatric unit. Conversely, non-compliance was the most frequent cause of graft failure (n=5; 83.3%) in patients experiencing graft failure during the adolescent period and treated in the adult unit; Figure 3.8 and Table 3.5.

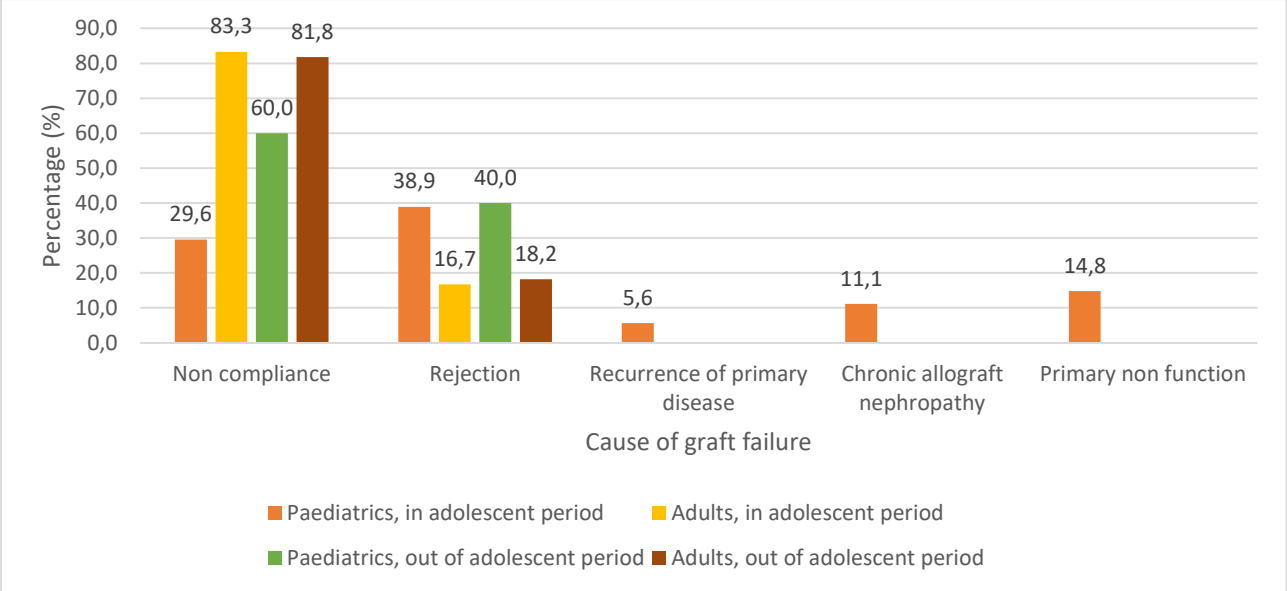


Figure 3.8: Distribution of the *cause of graft failure* in and out of the adolescent period, comparing paediatric and adult units for the patient data

Of the 98 patients with graft failure, 69 (70.4%) grafts were from a DD, and 29 (29.6%) were from an RLD. In the RLD category, the relationship of the donor to the patient, was the mother in 16 (55.2%), the father in 8 (27.6%), and a sibling in 3 (10.3%). The donor was unknown in 2 (6.9%) of the patients. Immunosuppressive Regimens 1 and 2 were used in 88 (89.7%) of the patients that experienced graft failure; Figure 3.9 and Table 3.5.

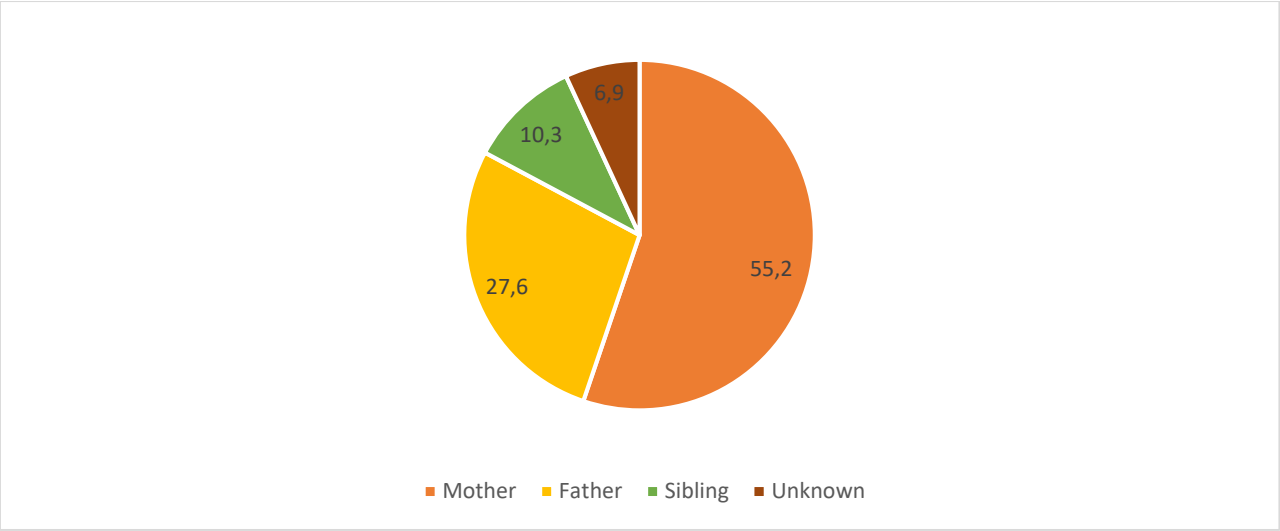


Figure 3.9: Pie chart illustrating the distribution of the donors for the RLD *overall*

Of the 60 patients with graft failure during the adolescent period, the majority (n=44; 73.3%) had DD transplants. In the 16 patients with failed RLD grafts, the patient's mother was the donor in 10 (62.4%), and father in 4 (25.0%) of the patients. The donor was the sibling and unknown in 1 (6.3%) each of the patients. Most of the patients experiencing graft failure during the adolescent period were on Regimens 1 and 2 (n=52; 86.7%); Figure 3.10 and Table 3.5.

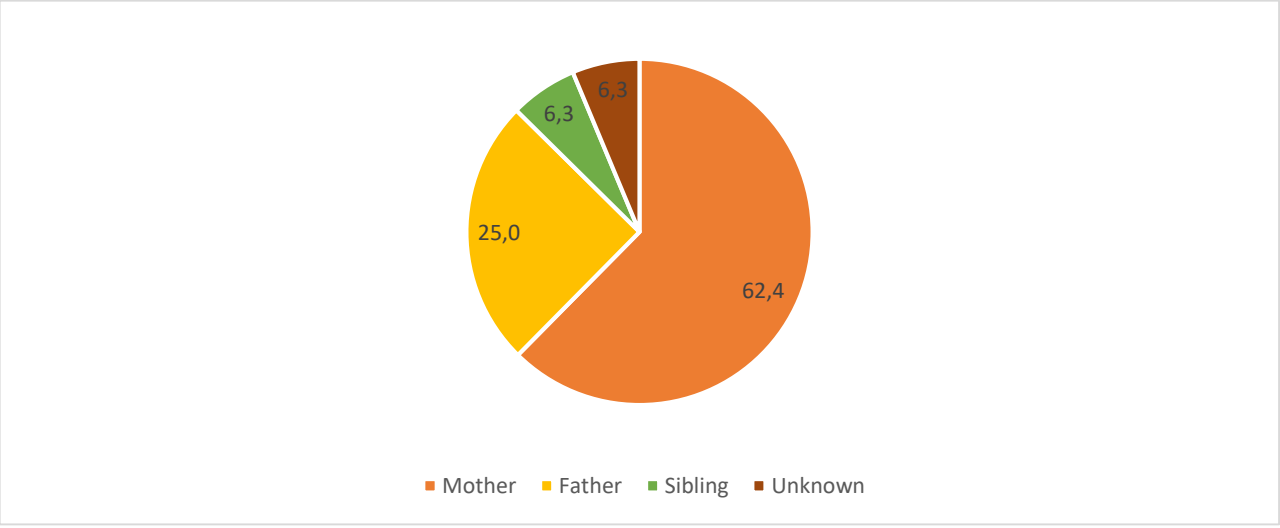


Figure 3.10: Pie chart illustrating the distribution of the donors for the RLD *during the adolescent period*

Table 3.5: Factors influencing graft failure (patient data in the study period)

Variable	Overall N = 98	In adolescent period N = 60		Out of adolescent period N = 38	
		Paediatric	Adult	Paediatric	Adult
Patients, n (%)	98	54 (90.0)	6 (10.0)	5 (13.2)	33 (86.8)
Age (years), median (IQR)	18.1 (15.6, 20.4)	15.7 (14.4, 17.6)	18.2 (17.7, 18.9)	20.2 (19.7, 20.9)	21.7 (20.0, 25.1)
Sex, n (%)					
Female	37 (37.8)	22 (40.7)	2 (33.3)	1 (20.0)	12 (36.4)
Male	61 (62.2)	32 (59.3)	4 (66.7)	4 (80.0)	21 (63.6)
Race, n (%)					
Black	58 (59.2)	31 (57.4)	6 (100.0)	1 (20.0)	20 (60.6)
White	31 (31.6)	19 (35.2)	0 (0.0)	4 (80.0)	8 (24.3)
Asian	4 (4.1)	3 (5.5)	0 (0.0)	0 (0.0)	1 (3.0)
Mixed race	5 (5.1)	1 (1.9)	0 (0.0)	0 (0.0)	4 (12.1)
Financial classification, n (%)					
Low SES [1]	7 (7.2)	3 (5.5)	2 (33.3)	0 (0.0)	2 (6.1)
Middle SES [2]	54 (55.1)	30 (55.6)	4 (66.7)	1 (20.0)	19 (57.6)
Private [3]	21 (21.4)	11 (20.4)	0 (0.0)	3 (60.0)	7 (21.2)
Foreign [4]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown [5]	16 (16.3)	10 (18.5)	0 (0.0)	1 (20.0)	5 (15.1)
Immunosuppressive regimen, n (%)					
Regimen 1 [6]	54 (55.1)	30 (55.6)	1 (16.7)	3 (60.0)	20 (60.6)
Regimen 2 [7]	34 (34.7)	16 (29.6)	5 (83.3)	1 (20.0)	12 (36.4)
Regimen 3 [8]	10 (10.2)	8 (14.8)	0 (0.0)	1 (20.0)	1 (3.0)
Cause, n (%)					
Non-compliance	51 (52.0)	16 (29.6)	5 (83.3)	3 (60.0)	27 (81.8)
Rejection	30 (30.6)	21 (38.9)	1 (16.7)	2 (40.0)	6 (18.2)
Recurrence primary disease	3 (3.1)	3 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic allograft nephropathy	6 (6.1)	6 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Primary non-function	8 (8.2)	8 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Low SES – patients on social pension, government grants (disability or social); [2] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [3] Private – patients on a medical aid, prisoner, suspect or road accident victims; [4] Foreign – foreign patients without documentation (illegally in South Africa); [5] Unknown – patients of unknown SES; [6] Regimen 1 – Azathioprine/cyclosporine/prednisone; [7] Regimen 2 – Tacrolimus/mycophenolate mofetil (MMF)/prednisone; [8] Regimen 3 – Cyclosporine/MMF/prednisone.

3.2.4.5 Death

Death which occurred in patients prior to entering the adolescent period (n=5), were excluded from the study. There were 12 deaths which occurred during the study period overall, 8 (66.7%) of which occurred in the paediatric unit, and 4 (33.3%) of which occurred in the adult unit. Of the deaths which occurred in the paediatric unit, 7 (87.5%) were during the adolescent period, and 1 (12.5%) was out of the adolescent period (the patient was >19 years old). In the adult unit, all 4 deaths occurred out of the adolescent period (age >19 years); Table 3.6.

All 7 deaths which occurred during the adolescent period occurred while the patient was receiving care from the paediatric unit. Most of these deaths (n=5; 71.4%) were related to graft failure. The other 2 (28.6%) patients died of septicaemia. The median age of death during the adolescent period was 15.3 years old (IQR: 13.1 to 18.0), with a median number of days from the date of transplant to the date of death of 906.5 days (IQR: 301.0 to 1451.5). Five (71.4%) of the patients that died were of black race. Four (57.1%) of the patients had congenital anomalies of the urogenital tract, 2 (28.6%) had glomerulonephritis, and 1 (14.3%) had lupus nephritis; Table 3.6.

Five (71.4%) of the 7 patients that died in the adolescent period were transplanted in the adolescent period, and 2 (28.6%) were transplanted prior to the adolescent period. Four (57.1%) transplants were during the 1990's, and 3 (42.9%) were during the 2000's. All 7 patients who demised had DD transplants, and had been on immunosuppressive Regimen 2. Four (57.1%) of the cases received one transplant prior to death, 1 (14.3%) received two grafts and 2 (28.6%) received three grafts in total; Table 3.6.

Table 3.6: Characteristics of the patients who demised during the study period

Variable	**Overall** [1] **N=162**	**Patients who demised in the study period N=12**	
		In adolescent period [2]	**Out adolescent period** [3]
Patients who demised, n (%)	12 (7.4)	7 (58.3)	5 (41.7)
Age (years), median (IQR)	18.0 (14.2, 19.5)	15.3 (13.1, 18.0)	19.5 (19.5, 27.6)
	N=12	**N=7**	**N=5**
Sex, n (%)			
Female	3 (25.0)	2 (28.6)	1 (20.0)
Male	9 (75.0)	5 (71.4)	4 (80.0)
Race, n (%)			
Black	7 (58.4)	5 (71.4)	2 (40.0)
White	4 (33.3)	1 (14.3)	3 (60.0)
Asian	1 (8.3)	1 (14.3)	0 (0.0)
Mixed race	0 (0.0)	0 (0.0)	0 (0.0)
Financial classification, n (%)			
Low [4]	0 (0.0)	0 (0.0)	0 (0.0)
Middle [5]	7 (58.4)	4 (57.1)	3 (60.0)
Private [6]	1 (8.3)	0 (0.0)	1 (20.0)
Foreign [7]	0 (0.0)	0 (0.0)	0 (0.0)
Not known [8]	4 (33.3)	3 (42.9)	1 (20.0)
Decade transplanted during			
1990's	9 (75.0)	4 (57.1)	5 (100.0)
2000's	3 (25.0)	3 (42.9)	0 (0.0)
Transplanted in adolescence, n (%)			
Yes	10 (83.3)	5 (71.4)	5 (100.0)
No	2 (16.7)	2 (28.6)	0 (0.0)
Type, n (%)			
RLD [9]	2 (16.7)	0 (0.0)	2 (40.0)
DD [10]	10 (83.3)	7 (100.0)	3 (60.0)

[1] Overall – total number of patients receiving a renal transplant; [2] In the adolescent period – transferred to adults between ages 10 to 19 years old; [3] Out the adolescent period – transferred to adults after 19 years old; [4] Low SES – patients on social pension, government grants (disability or social); [5] Middle SES – patients with an income less than R72 000.00 per annum and households with an income less than R100 000.00 per annum; [6] Private – patients on a medical aid, prisoner, suspect or road accident victims; [7] Foreign – foreign patients without documentation (illegally in South Africa); [8] Unknown – patients of unknown SES; [9] RLD – related living donor; [10] DD – deceased donor.

3.2.4.6 Non-compliance

In both the paediatric and adult units combined, 47 (29.0%) patients were non-compliant during the study period. Fifteen (31.9%) patients had one episode of non-compliance, 14 (29.8%) had two episodes, 8 (17.0%) had three episodes of non-compliance and 10 (21.3%) had four or more episodes of non-compliance.

The majority (n=27; 57.4%) of the patients that were non-compliant, were male. Furthermore, most (n=23; 48.9%) of the non-compliant patients were black, followed by (n=19; 40.4%) white patients, and most (n=30; 63.8%) were of the middle SES category. Twenty-nine (61.7%) patients who were non-compliant had congenital renal diagnoses, 11 (23.4%) had glomerular disease, and 7 (14.9%) had other diagnoses; Table 3.7.

The majority (n=35; 74.5%) of the non-compliant patients were transplanted during adolescence. Nineteen (40.4%) and 28 (59.6%) of the patients were transplanted in the 1990's and 2000's respectively. Most (n=35; 74.5%) of the non-compliant patients received one renal transplant during the study period; Table 3.7.

With respect to the immunosuppressive regimen, for Regimens 1 and 2, there were 22 (46.8%) non-compliant patients each on these regimens, and 3 (6.4%) patients were on regimen 3. Furthermore, 25 (53.2%) had received their graft from a DD. Of the 22 (46.8%) non-compliant patients who had received a graft from an RLD, 12 (54.5%) received the graft from their mother, 8 (36.4%) received their grafts from their father; Table 3.7.

In patients who were non-compliant, the final outcome during the adolescent period comprised graft failure (n=19; 40.4%), transfer to another facility (n=7; 14.9%) death (n=2; 4.3%) or lost to follow up (n=2; 4.3%). Seventeen (36.1%) of the patients who were non-compliant had preserved graft function. (Figure 3.11 and Table 3.7).

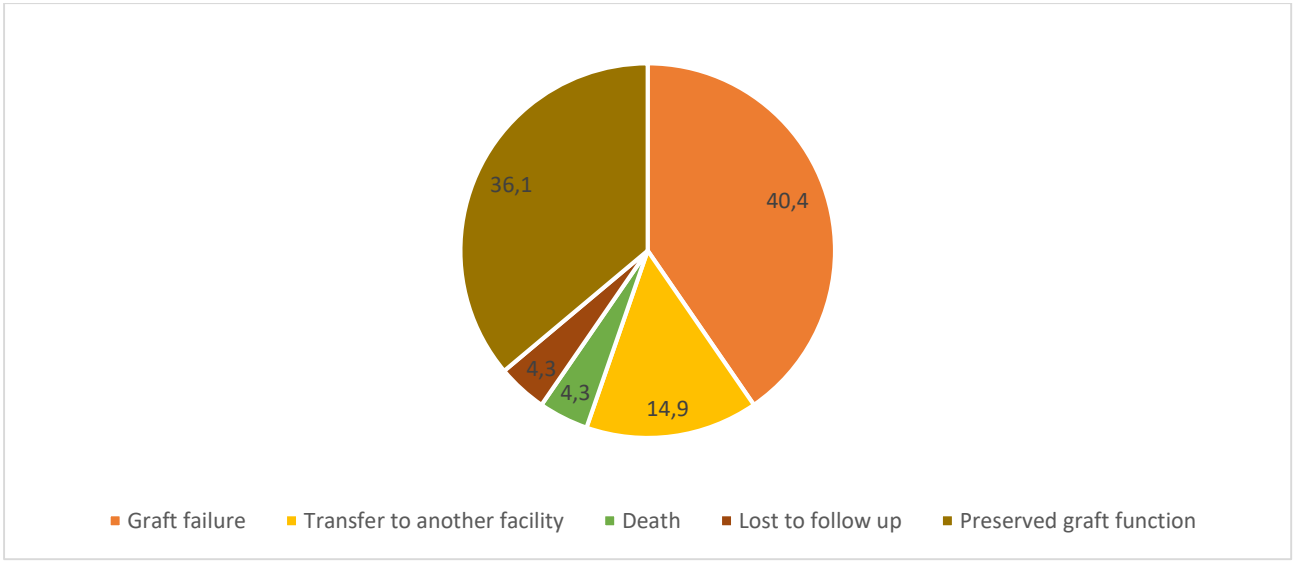


Figure 3.11: Pie chart showing the *final outcomes during the adolescent period* for the non-compliant patients

Table 3.7: Non-compliant episodes for both the paediatric and adult units

Characteristic	Paediatric data N=28	Adult data N=19	Paediatric and adult data N=47
Number of episodes of non-compliance			
1	9 (32.2)	6 (31.6)	15 (31.9)
2	8 (28.5)	6 (31.6)	14 (29.8)
3	5 (17.9)	3 (15.8)	8 (17.0)
≥4	6 (21.4)	4 (21.0)	10 (21.3)
Sex, n (%)			
Female	12 (42.9)	8 (42.1)	20 (42.6)
Male	16 (57.1)	11 (57.9)	27 (57.4)
Racial group, n (%)			
Black	10 (35.7)	13 (68.4)	23 (48.9)
White	16 (57.2)	3 (15.8)	19 (40.4)
Asian	0 (0.0)	1 (5.3)	1 (2.1)
Mixed race	2 (7.1)	2 (10.5)	4 (8.6)
Financial classification, n (%)			
Low SES	2 (7.1)	2 (10.5)	4 (8.5)
Middle SES	17 (60.7)	13 (68.4)	30 (63.8)
Private	6 (21.4)	3 (15.8)	9 (19.2)
.Foreign	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	3 (10.8)	1 (5.3)	4 (8.5)
Diagnosis (combined), n (%)[17]			
Glomerular disease group [1]	18 (64.2)	11 (57.9)	29 (61.7)
Congenital group [2]	5 (17.9)	6 (31.6)	11 (23.4)
Other group [3]	5 (17.9)	2 (10.5)	7 (14.9)
Transplanted during the adolescent period, n (%)			
Yes	21 (75.0)	14 (73.7)	35 (74.5)
No	7 (25.0)	5 (26.3)	12 (25.5)
Decade transplanted during, n (%)			
1990's	12 (42.9)	7 (36.8)	19 (40.4)
2000's	16 (57.1)	12 (63.2)	28 (59.6)
Total number of renal transplants, during the study period, n (%)			
1	19 (67.9)	16 (84.2)	35 (74.5)
≥2	9 (32.1)	3 (15.8)	12 (25.5)
Immunosuppressive regimen, n (%)			
Regimen 1 (A/C/P) [4]	14 (50.0)	8 (42.1)	22 (46.8)
Regimen 2 (T/M/P) [5]	12 (42.8)	10 (52.6)	22 (46.8)
Regimen 3 (C/M/P) [6]	2 (7.2)	1 (5.3)	3 (6.4)
Type of renal transplant, n (%)			
RLD [7]	10 (35.7)	12 (63.3)	22 (46.8)
DD [8]	18 (64.3)	7 (36.7)	25 (53.2)
Donor, if RLD [9], n (%)			
Mother	5 (50.0)	7 (58.3)	12 (54.5)
Father	3 (30.0)	5 (41.7)	8 (36.4)
Sibling	2 (20.0)	0 (0.0)	2 (9.1)
Aunt	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Final outcome of the patients, during the adolescent period, n (%)			
Graft failure	18 (64.3)	1 (5.3)	19 (40.4)
Death	1 (3.6)	1 (5.3)	2 (4.3)
Transfer to another facility	4 (14.3)	3 (15.8)	7 (14.9)
Lost to follow up	0 (0.0)	2 (10.4)	2 (4.3)
Preserved graft function [10]	5 (17.8)	12 (63.2)	17 (36.1)

[1]Glomerular disease group – APSGN, FSGS, FSH, GN and RPGN; [2]Congenital disease group – ARPKD, congenital nephrotic syndrome, dysplastic kidneys, PUV, primary reflux nephropathy, and VUR; [3]Other – HUS, SLE, medullary cystic, Takayasu's arteritis, Lawrence Moon Body Biedl, HSP, and primary hyperoxalosis; [4]Regimen 1 – A/C/P – Azathioprine, cyclosporine, prednisone; [5]Regimen 2 – T/M/P – Tacrolimus, MMF, prednisone; [6]Regimen 3 – C/M/P – Cyclosporine, MMF, prednisone; [7]RLD – related living donor; [8]DD – deceased donor; [9]Donor, if RLD; [10]Preserved graft function - patients had a functioning graft at the conclusion of the study period.

3.2.4.7 Rejection episodes and renal biopsies

There were 62 (38.3%) adolescent patients, in the paediatric unit, who had rejection episodes in the study period. Of these patients, 2 (3.2%) had rejection episodes prior to the adolescent period as well. In total, of the 162 patients, 5 (3.1%) had had rejection episodes prior to the adolescent period; Table 3.9.

A total of 115 rejection episodes occurred during the study period in the paediatric unit, in the patients in the adolescent period, 62 (53.9%) of whom had one rejection episode, and 27 (23.5%) patients had two rejection episodes. From the group of patients who had three, and four or more rejection episodes, each group comprised 13 (11.3%) patients; Table 3.9.

The median age of the patients who had one rejection episode was, 15.2 years (IQR: 13.3 to 16.6). In those patients who had a second, and third rejection episode, the median ages were, 14.9 years (IQR: 12.1 to 15.7) and 14.5 years (IQR: 12.1 to 15.9), respectively. In the group of patients who had four or more rejection episodes, the median age was 15.2 years (IQR: 13.5 to 16.2). The median number of days from the date of transplant to the date of the first rejection episode, was 671 days (IQR: 327 to 1519); Table 3.9.

Table 3.8: Rejection episodes in the patient dataset (paediatric unit)

Variable	**Number of rejection episodes during the adolescent period N=115**			
	1	**2**	**3**	**≥4**
Number of patients, n (%)	62 (53.9)	27 (23.5)	13 (11.3)	13 (11.3)
Age (years), median (IQR)	15.2 (13.3, 16.6)	14.9 (12.1, 15.7)	14.5 (12.1, 15.9)	15.2 (13.5, 16.2)
Number of days from transplant to date of rejection episode, median (IQR) [1]	671 (327, 1519)	1113 (630, 1829)	1211 (795, 2382)	1656 (1118, 2306)
Sex, n (%)				
Female	29 (46.8)	10 (37.0)	4 (30.8)	2 (15.4)
Male	33 (53.2)	17 (63.0)	9 (69.2)	11 (84.6)
Race, n (%)				
Black	32 (51.6)	13 (48.1)	8 (61.5)	8 (61.5)
White	26 (41.9)	13 (48.1)	5 (38.5)	5 (38.5)
Asian	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed race	3 (4.8)	1 (3.8)	0 (0.0)	0 (0.0)
Type of transplant, n (%)				
RLD	29 (46.8)	13 (48.1)	5 (38.5)	4 (30.8)
DD	33 (53.2)	14 (51.9)	8 (61.5)	9 (69.2)
Immunosuppressive regimen, n (%)				
Regimen 1 [2]	22 (35.5)	7 (25.9)	2 (15.4)	2 (15.4)
Regimen 2 [3]	31 (50.0)	16 (59.3)	9 (69.2)	8 (61.5)
Regimen 3 [4]	9 (14.5)	4 (14.8)	2 (15.4)	3 (23.1)
Non-compliance, n (%)				
Yes	26 (41.9)	18 (66.7)	9 (69.2)	13 (100.0)
No	36 (58.1)	9 (33.3)	4 (30.8)	0 (0.0)

[1]Number of days from transplant to rejection episode – calculated from the date of transplant to date of rejection episode; [2]Regimen 1 – Azathioprine, cyclosporine, prednisone; [3]Regimen 2 – Tacrolimus, mycophenolate mofetil (MMF), prednisone; [4]Regimen 3 – Cyclosporine, MMF, prednisone.

Of the 62 adolescent patients who had rejection episodes in the paediatric unit, 27 (43.5%) renal biopsies were performed. Twenty-four (88.9%) patients had one renal biopsy, and 3 (11.1%) had two biopsies. The median age at first and second renal biopsy, was 15.9 years (IQR: 14.5 to 17.3) and 17.8 years (IQR: 15.9 to 18.0) respectively. Fourteen (58.3%) of the first renal biopsies demonstrated acute cell mediated rejection (T cell mediated rejection), and 4 (16.7%) showed antibody mediated

rejection (B cell mediated rejection). Recurrence of primary disease, and a combination of acute and antibody mediated rejection, were found in 1 (4.2%) each of the patients experiencing graft failure that had one renal biopsy. In 2 (8.3%) biopsies, calcineurin inhibitor (CNI) toxicity was demonstrated, and in 2 (8.3%) biopsies, histology demonstrated chronic allograft rejection and vascular infarct. The findings of the second renal biopsy were acute cell mediated rejection (n=1), CNI toxicity (n=1), and unknown cause of rejection (failed renal biopsy; n=1) (Figure 3.12 and Table 3.10).

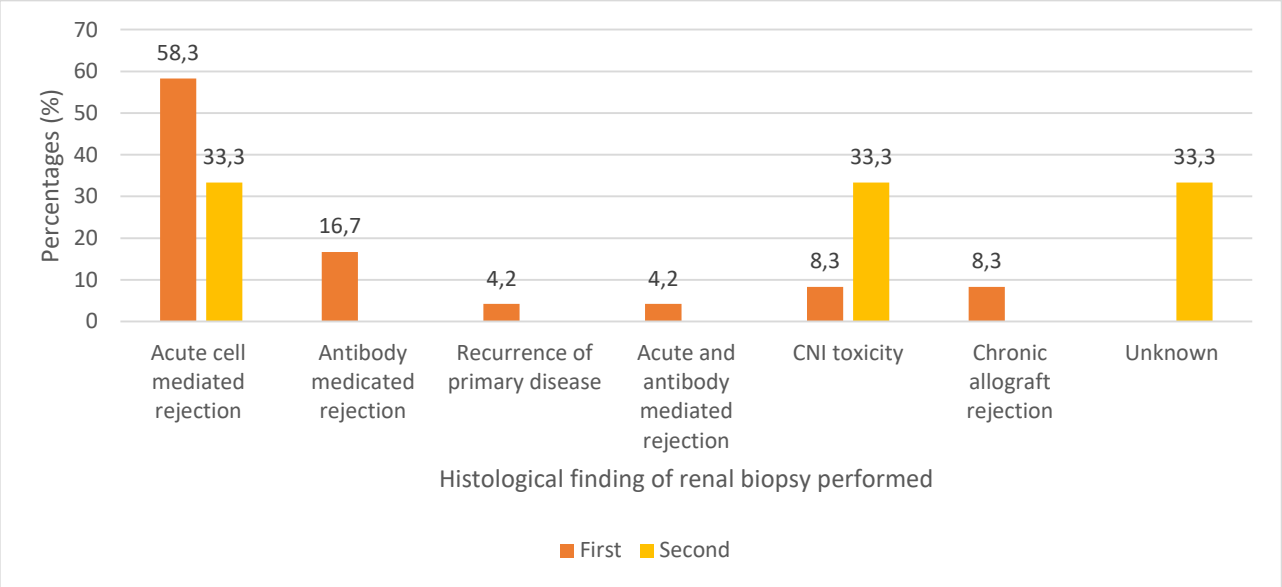


Figure 3.12: *Histological findings* of renal biopsies performed

The median number of days from the date of transplant to the date of the first renal biopsy was 378 days (IQR: 109 to 1192), compared to 1589 days (IQR: 494 to 2025) for the second renal biopsy (Table 3.10).

Of the 54 patients transferred to the adult unit during the adolescent period, 14 rejection episodes occurred in the study period. Of these, 11 (78.6%) patients had one rejection episode, and 3 (21.4%) patients had two episodes. The median age at which the first and second rejection episodes occurred

were similar; 17.2 years (IQR: 16.5 to 17.9), and 17.3 years (IQR: 17.3 to 17.9) respectively. The median number of days from the date of transplant to the date of first and second rejection episodes in the adult unit were 1426 days (IQR: 705 to 2683) and 1539 days (IQR: 420 to 2775), respectively. With respect to the number of days from the date of transfer of the patient from the paediatric nephrology unit to the date of the rejection episode (10 patients, 1 patient had missing data), the median number of days was 148 days (IQR: 120 to 304) for the first rejection episode, and 281 days (IQR: 81 to 417) for the second rejection episode (Table 3.10).

Table 3.9: Rejection episodes in the patient dataset (adult unit)

Variable	**Number of rejection episodes during the adolescent period N=14**	
Rejection episodes	**1**	**2**
Number of patients, n (%)	11 (78.6)	3 (21.4)
Age (years), median (IQR)	17.2 (16.5, 17.9	17.3 (17.3, 17.9
Number of days from transplant to date of rejection episode, median (IQR) [1]	1426 (705, 2683	1539 (420, 2775
Sex, n (%)		
Female	5 (45.5)	1 (33.3)
Male	6 (54.5)	2 (66.7)
Race, n (%)		
Black	8 (72.7)	3 (100.0)
White	3 (27.3)	0 (0.0)
Asian	0 (0.0)	0 (0.0)
Mixed race	0 (0.0)	0 (0.0)
Type of transplant, n (%)		
RLD	4 (36.4)	1 (33.3)
DD	7 (63.6)	2 (66.7)
Immunosuppressive regimen, n (%)		
Regimen 1 [2]	3 (27.3)	0 (0.0)
Regimen 2 [3]	8 (72.7)	3 (100.0)
Regimen 3 [4]	0 (0.0)	0 (0.0)
Non-compliance, n (%)		
Yes	3 (27.3)	1 (33.3)
No	8 (72.7)	2 (66.7)

[1]Number of days from transplant to rejection episode – calculated from the date of transplant to date of rejection episode; [2]Regimen 1 – Azathioprine, cyclosporine, prednisone; [3]Regimen 2 – Tacrolimus, mycophenolate mofetil (MMF), prednisone; [4]Regimen 3 – Cyclosporine, MMF, prednisone.

Of the 14 adolescent patients who had rejection episodes in the adult unit, 9 (64.3%) had renal biopsies performed. Seven (77.8%) had one renal biopsy, with the most frequent finding (n=4; 57.1%) being acute cell mediated rejection. The median age at which the first biopsy was performed was 17.0 years (IQR: 16.4 to 17.6). Two (22.2%) patients had a second renal biopsy, both of whom were

demonstrated to have acute cell mediated rejection on histological examination. The median age at which the second biopsy occurred was 17.2 years (IQR: 17.0 to 17.3). The median number of days from the date of transplant to the date of first and second renal biopsy were 1419 days (IQR: 695 to 2683) and 1812 days (IQR: 848 to 2775), respectively.

3.2.5 Survival analysis

Overall 1-year, 3-year, 5-year, and 10-year patient survival amongst the whole study group was 98.8%, 97.6%, 95.1%, and 93.9% respectively. The 1-year, 3-year, 5-year, and 10-year patient survival (98.5%, 97.7%, 95.3%, and 93.8%) of patients only transplanted during the adolescent period compared similarly to those patients transplanted prior to the adolescent period, and subsequently entered adolescence with a functioning transplant (100.0%, 97.1%, 94.1%, and 94.1% respectively) (Table 3.10).

Table 3.10: Survival estimates

	Overall (%)	Transplant during adolescence (%)	Transplant prior to adolescence, entered adolescence with functioning graft (%)
1-year	98.8	98.5	100.0
3-year	97.6	97.7	97.1
5-year	95.1	95.3	94.1
10-year	93.9	93.8	94.1

Death occurred in 12 (7.4%) of the 162 patients during the study period, however, 7 (4.3%) patients demised during the adolescent period. All of the adolescent period deaths occurred while the patients were following up in the paediatric nephrology unit. There were 7 deaths in children during the adolescent period and numbers were too small to analyse successfully using a Cox Proportional Hazards model. Figure 3.13 shows the unadjusted survival curve over time. A median survival could

not be reached when constructing the survival analysis due to the low number of deaths in the study period.

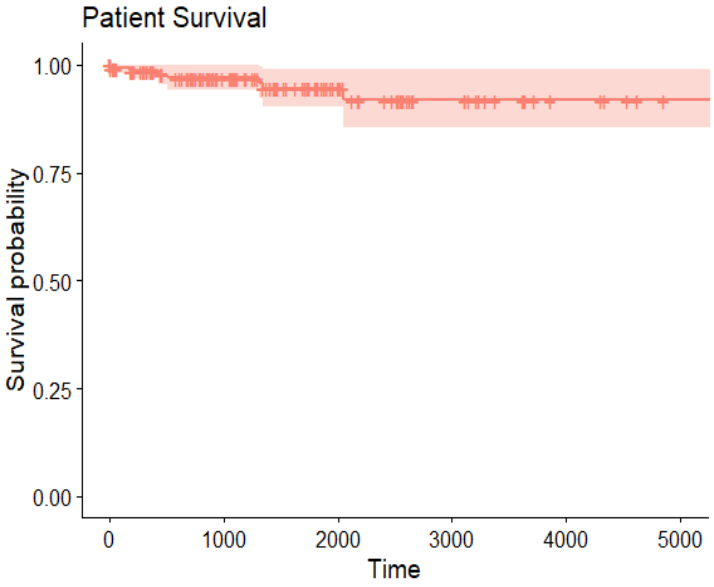


Figure 3.13: Kaplan-Meier curve of the *unadjusted patient survival analysis*

Neither sex (p-value=0.52) nor race (white group compared to non-white group; p-value=0.12) contributed to patient survival. Survival of patients of foreign or unknown SES classification, had significantly poorer survival compared to the reference group (patients of low SES, middle SES, or private classification) (p-value=0.004); Figure 3.14, and Table 3.11.

When comparing the congenital, glomerular, and other disease group, there was no significant contribution to patient survival (p-value=0.13). However, with the sub-analysis comparing patient survival between the glomerular disease group to the other diagnosis groups, significantly worse patient survival was observed in the group with glomerular disease (p-value=0.037); Figure 3.14, and Table 3.11.

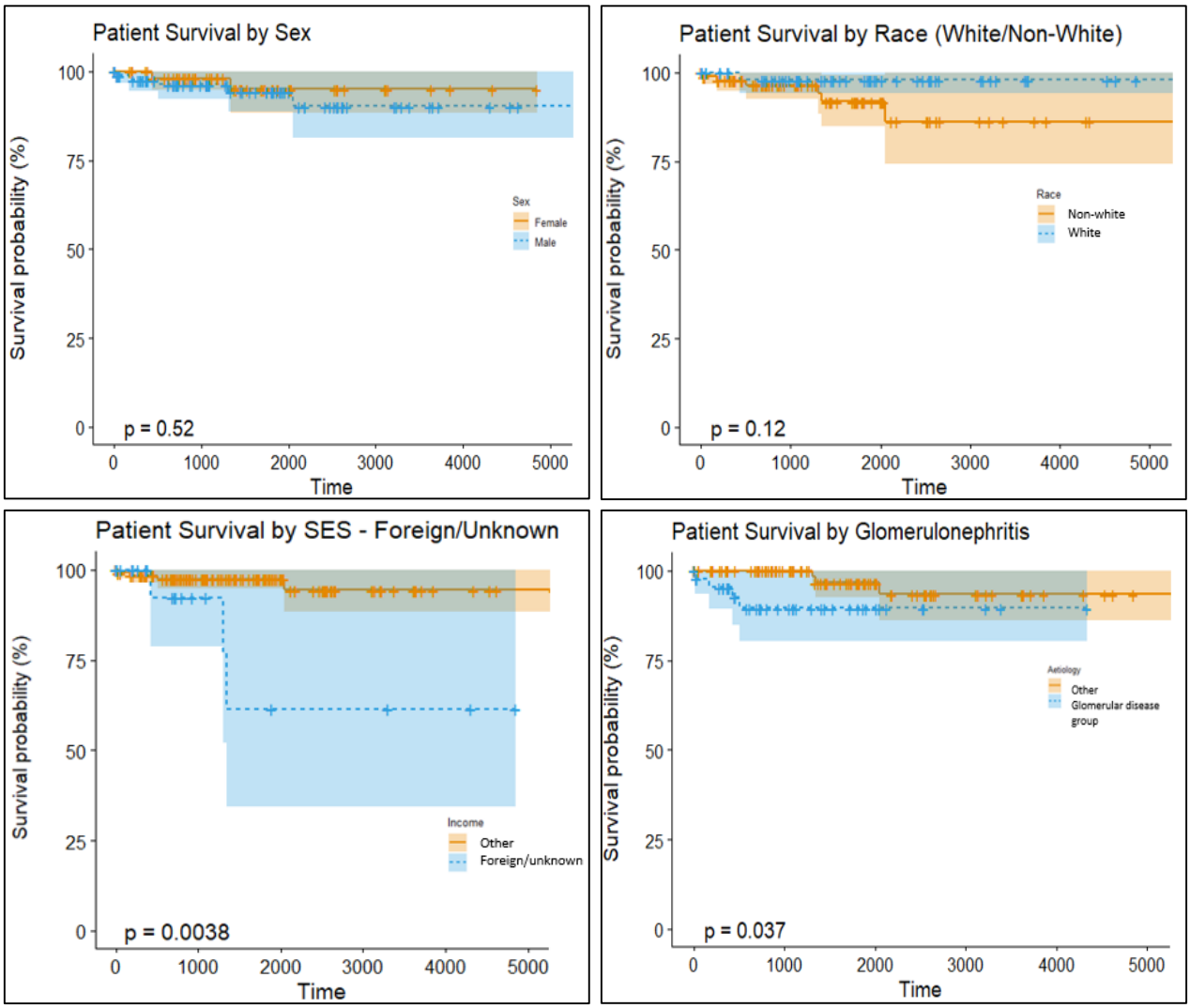


Figure 3.14: Kaplan-Meier curves showing patient survival by *the demographic characteristics*

Transplant factors that did not to contribute significantly to patient survival included immunosuppressive regimen (p-value=0.36), whether or not patients were transplanted during the adolescent period (p-value=0.74), and the decade during which the transplant occurred in (p-value=0.39). The total number of renal transplants received by the patient, was not found to contribute significantly to overall patient survival (p-value=0.23); Figure 3.15, and Table 3.11.

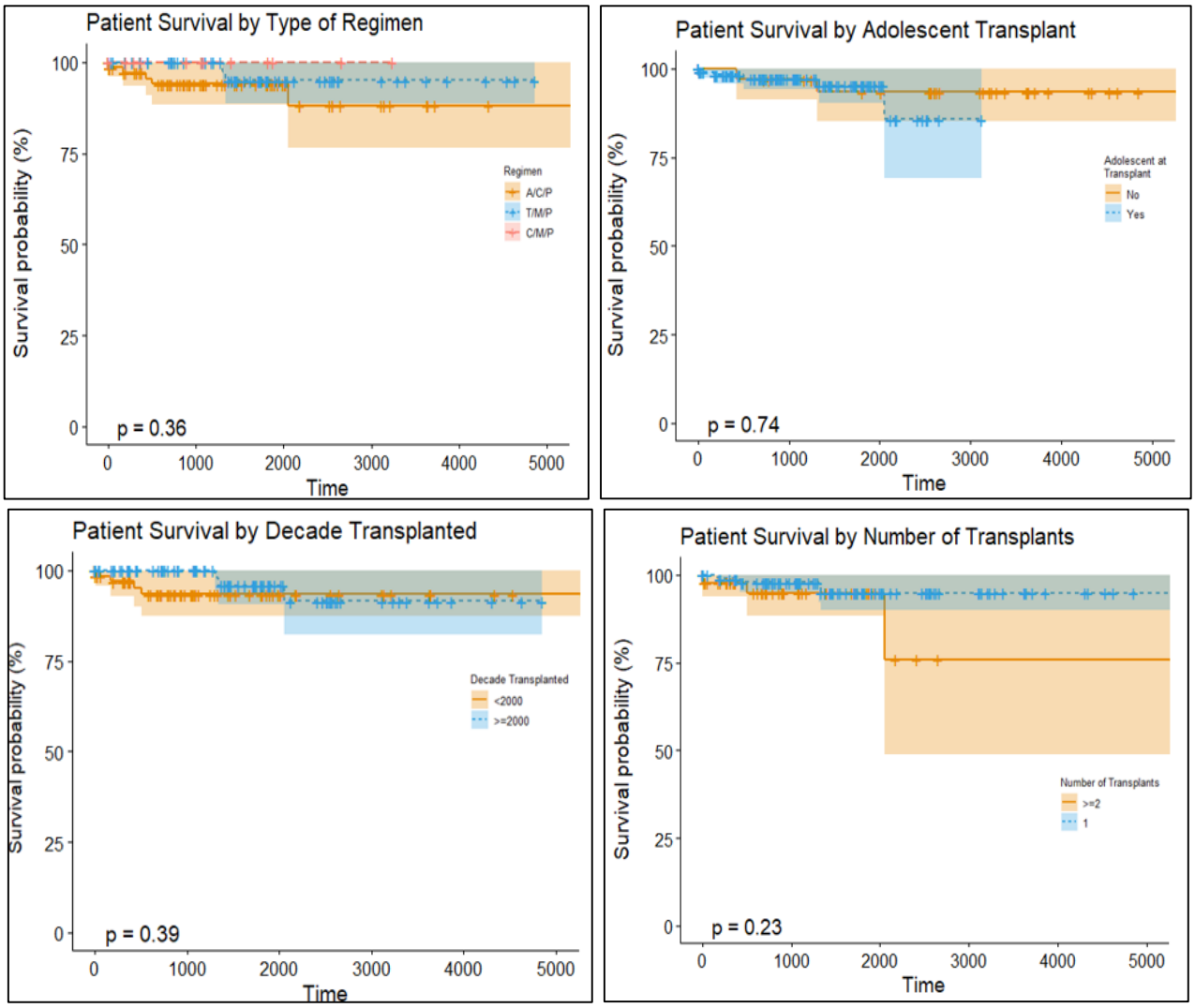


Figure 3.15: Kaplan-Meier curves showing patient survival by *transplant characteristics*

Survival of RLD transplant recipients was significantly better than that of DD recipients (p-value=0.019). There were no deaths during the adolescent period amongst patients who were transferred to the adult nephrology unit during the study period. Patients who were transferred to the adult unit had significantly better survival compared to the patients who remained in the paediatric unit (p-value=0.028); Figure 3.16, and Table 3.11.

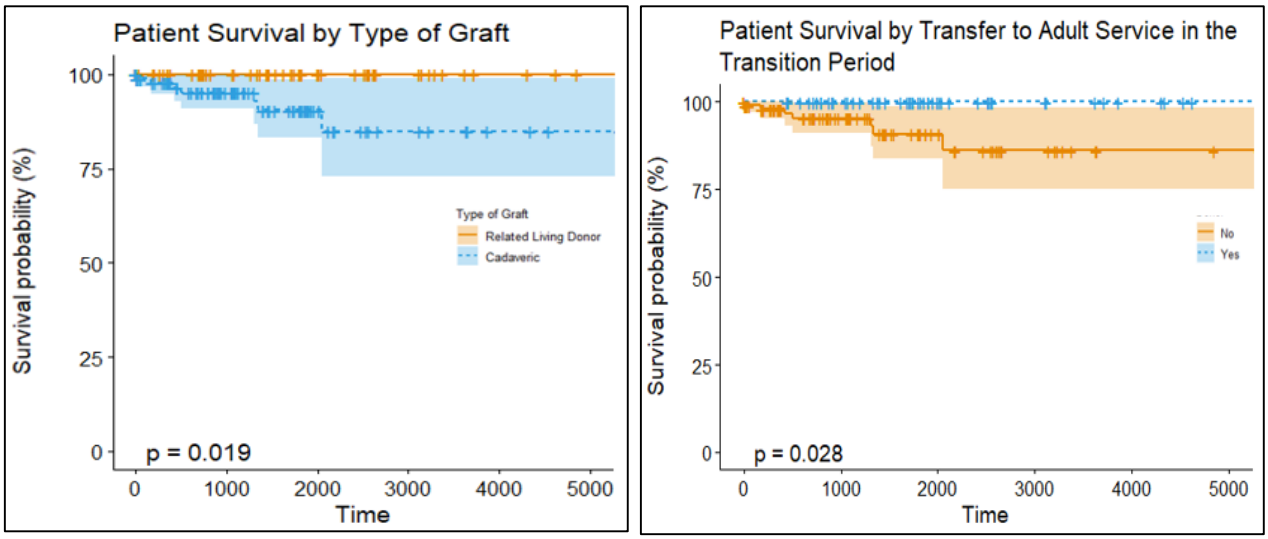


Figure 3.16: Kaplan-Meier curve showing patient survival by *type of graft and transfer to the adult unit*

Analysis of the eGFR values, showed that baseline eGFR (taken at transplant), did not contribute significantly to patient survival (p-value=0.95). However, the eGFR taken at graft failure (final eGFR), showed that patients with eGFR <10mL/min/1.73m^2, had worse patient outcomes compared to the patients with a final eGFR of ≥10mL/min/1.73m^2 (p-value=0.001); Figure 3.17, and Table 3.11.

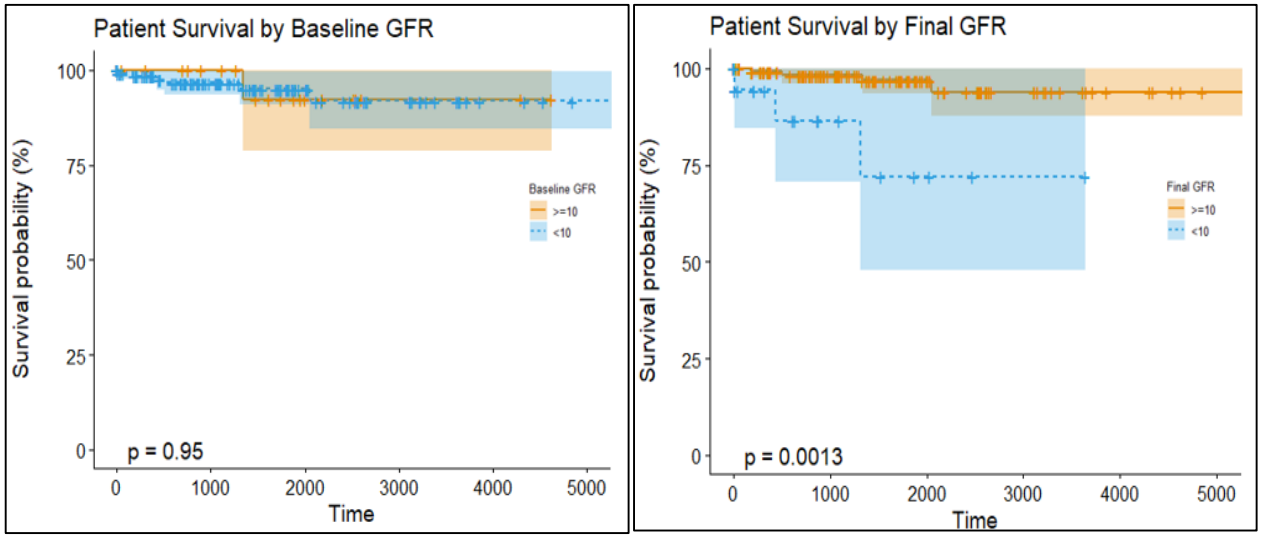


Figure 3.17: Kaplan-Meier curves showing patient survival by *baseline eGFR and final eGFR*

In patients who were non-compliant at any point during the study period (paediatric or adult unit), had poorer survival compared to those patients who had no episodes of non-compliance, although not statistically significant (p-value=0.086); Figure 3.18 and Table 3.11.

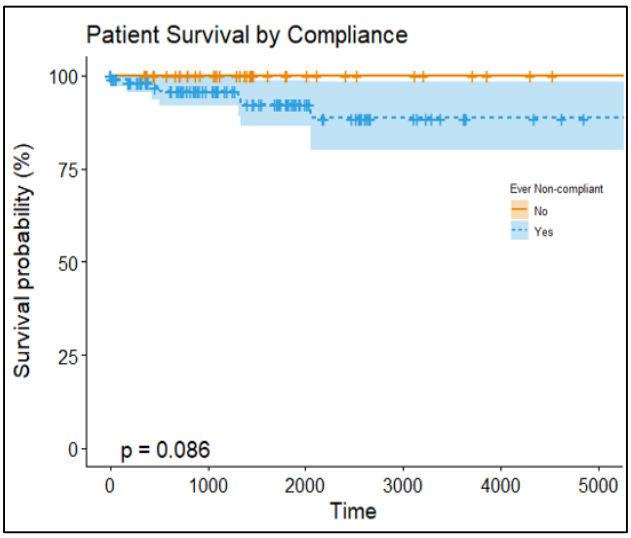


Figure 3.18: Kaplan-Meier curves showing patient survival by *compliance*

Rejection episodes, prior to the adolescent period (p-value=0.55), or during the adolescent period (p-value=0.97), did not contribute significantly to patient survival; Figure 3.19, and Table 3.11.

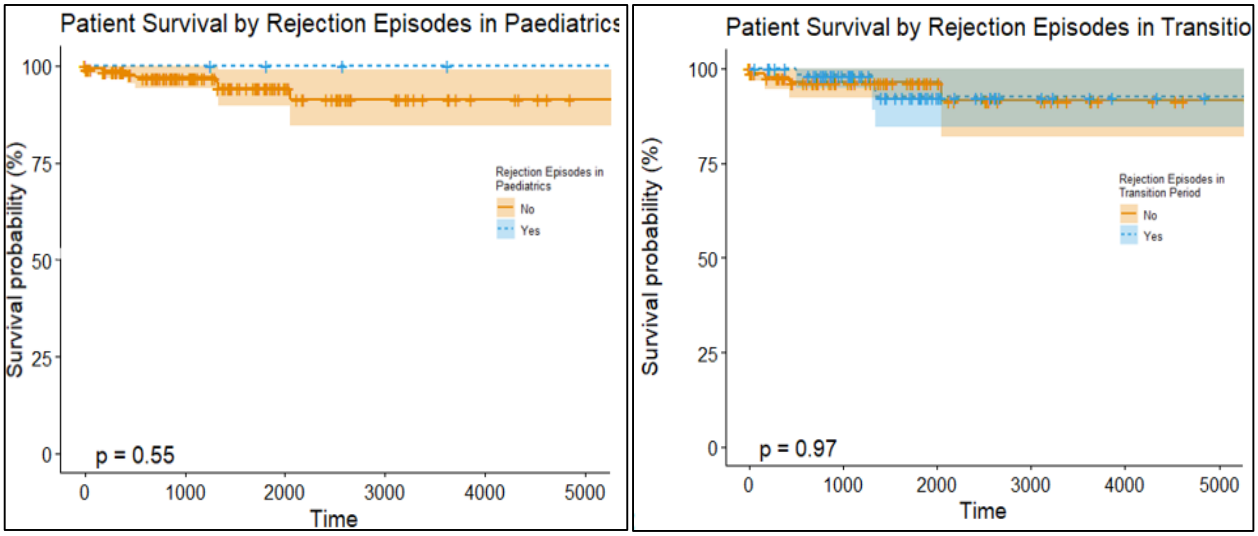


Figure 3.19: Kaplan-Meier curves showing patient survival by *rejection episodes*

Table 3.11: Univariate analysis constructed from Cox Proportional Hazards modelling: Patient Survival

Variable	**Demised N=7 n (%)**	**Alive N=155 n (%)**	**HR (95% CL of HR)** [1]	***P* value** [2]
Sex				
Male	5 (71.4)	92 (59.4)	1.7 (0.3 – 8.8)	0.528
Female	2 (28.6)	63 (40.6)	Ref.	
Race				
White	1 (14.3)	62 (40.0)	0.2 (0.02 – 1.8)	0.157
Non-white	6 (85.7)	93 (60.0)	Ref.	
Financial classification				
Foreign or unknown	3 (42.9)	21 (13.5)	6.9 (1.5 – 31)	0.012
Other SES groups	4 (57.1)	134 (86.5)	Ref.	
Diagnosis				
Glomerulonephritis group	4 (57.1)	43 (27.8)	4.4 (1.0 – 20.0)	0.056
Other diagnoses, combined	3 (42.9)	112 (72.2)	Ref.	
Transplanted during adolescent period				
Yes	5 (71.4)	123 (79.4)	1.3 (0.2 – 7.7)	0.738
No	2 (28.6)	32 (20.6)	Ref.	
Type of renal transplant				
DD [3]	7 (100.0)	94 (60.6)	No estimate	0.998
RLD [4]	0 (0.0)	61 (39.4)	Ref.	
Number of transplants in study period				
<2	4 (57.1)	105 (67.7)	0.4 (0.09 – 1.8)	0.242
≥2	3 (42.9)	50 (32.3)	Ref.	
Decade transplanted				
2000's	3 (42.9)	83 (53.5)	0.5 (0.1 – 2.3)	0.395
1990's	4 (57.1)	72 (46.5)	Ref.	
Immunosuppressive regimen (T/M/P)				
T/M/P (Regimen 2) [5]	2 (28.6)	66 (42.6)	0.4 (0.09 – 2.3)	0.324
Regimens 1 and 3 [6]	5 (71.4)	89 (57.4)	Ref.	
Rejection episodes in the adolescent period				
Yes	3 (42.9)	61 (39.4)	1.0 (0.2 – 4.3)	0.967
No	4 (57.1)	94 (60.6)	Ref.	
eGFR values [8]				
At time of transplant (eGFR < 10)	-	-	1.1 (0.1 – 8.9)	0.948
Final eGFR taken during study period (eGFR < 10)	-	-	8.1 (1.8 – 37.0)	0.007

[1] Univariate – HR (95% CL of HR) - calculated hazards ratio with 95% confidence limit using Cox proportional hazards analysis (adjusted for transfer to another facility and LTFU); [2]*P* value – using Log rank test and Kaplan-Meier Curve; [3]DD – Deceased donor; [4]RLD – related living donor; [5]T/M/P (Regimen 2) – Tacrolimus, mycophenolate mofotil (MMF), prednisone; [6]A/C/P (Regimen 1) – Azathioprine, cyclosporine, prednisone; C/M/P (Regimen 3) – Cyclosporine, MMF, prednisone; [8]eGFR – estimated glomerular filtration rates. Ref. = referent.

In multivariate analysis, only SES (p-value=0.009) and final eGFR (taken at the time of graft failure) (p-value=0.004) contributed significantly to patient survival (AIC 55.7; p-value 0.024); Table 3.12.

Table 3.12: Multivariate analysis for patient survival

Variable	**Demised N=7 n (%)**	**Alive N=155 n (%)**	**HR (95% CL of HR)** [1]	***P* value** [2]
Race				
White	1 (14.3)	62 (40.0)	0.19 (0.02 – 1.8)	0.146
Non-white	6 (85.7)	93 (60.0)	Ref.	
Financial classification				
Foreign or unknown [3]	3 (42.9)	21 (13.5)	9.5 (1.7 – 52.0)	0.009
Other SES groups [4]	4 (57.1)	134 (86.5)	Ref.	
Diagnosis				
Glomerulonephritis group	4 (57.1)	43 (27.8)	3.7 (0.7 – 19.0)	0.112
Other diagnoses, combined	3 (42.9)	112 (72.2)	Ref.	
Number of transplants in study period				
<2	4 (57.1)	105 (67.7)	0.4 (0.06 – 2.1)	0.263
≥2	3 (42.9)	50 (32.3)	Ref.	
eGFR values [5]				
Final eGFR taken during study period (eGFR <10)	-	-	14 (2.4 – 85)	0.004

[1]Multivariate analysis – HR (95% CL of HR) - calculated hazards ratio with 95% confidence limit using Cox proportional hazards analysis (adjusted for transfer to another facility and LTFU); [2]*P* value – using Log rank test and Kaplan-Meier Curve; [3]Foreign – foreign patients without documentation (illegally in South Africa), or unknown – patients of unknown SES; [4] Low SES – patients on social pension, government grants (disability or social); Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; Private – patients on a medical aid, prisoner, suspect or road accident victims; [5]eGFR – estimated glomerular filtration rates. Ref. = referent.

3.3 GRAFT CHARACTERISTICS

3.3.1 Demographics

The graft database included data on 213 grafts, 83 (39.0%) in female recipients and 130 (61.0%) in males. One hundred, fourteen (53.5%) grafts were in black patients, 73 (34.3%) in whites, 13 (6.1%) in Asians and 13 (6.1%) in patients of mixed race. The majority of the grafts (117; 54.9%) were in the middle SES group (Figure 3.20).

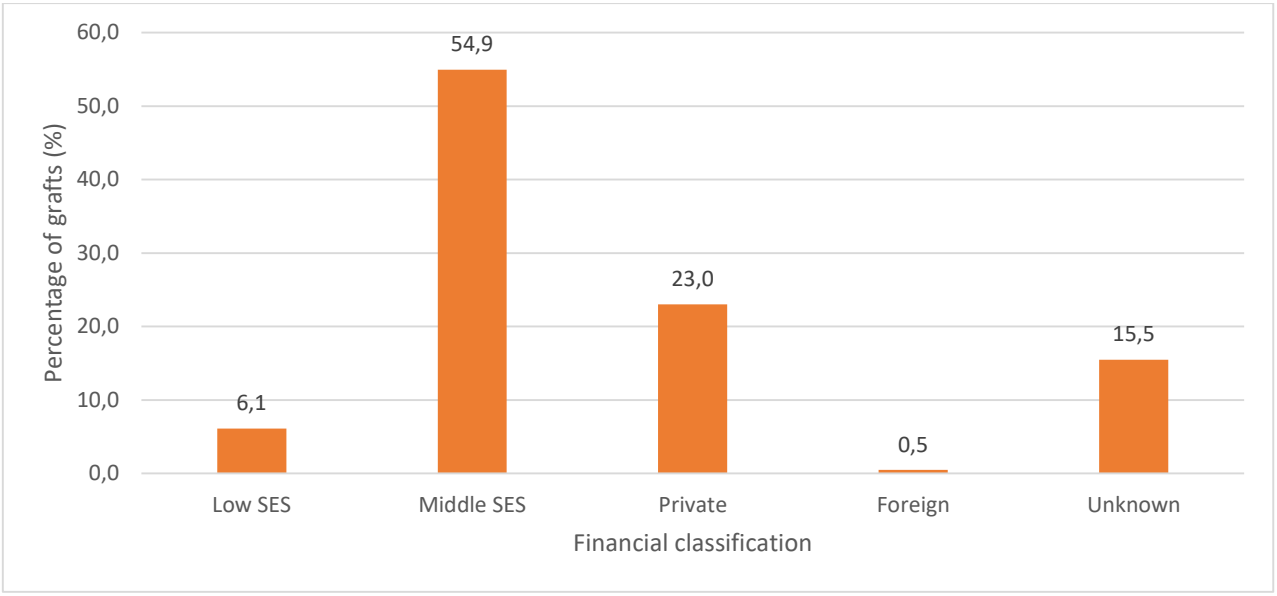


Figure 3.20: Frequency of each financial classification for graft data

3.3.2 Aetiology of CKD

The 'top 4' diagnoses among recipients in the graft dataset were dysplastic kidneys (n=32; 15.0%), PUV (n=30; 14.1%), FSGS (n=27; 12.7%) and congenital nephrotic syndrome (n=20; 9.4%), as was observed in the patient dataset (Section 3.2.2). Thereafter, the aetiologic diagnosis differed slightly from that seen in the patient dataset with FSH (n=20, 9.4%), primary reflux nephropathy (n=18; 8.5%), RPGN (n=14; 6.6%), ARPKD (n=12; 5.6%), GN (n=8; 3.8%) and HUS (n=7; 3.3%)

contributing to the balance of the ‘top 10’ underlying diagnoses. The ‘top 10’ diagnoses contributed to CKD in 88.3% (n=188) in recipients captured in the graft dataset (Table 3.13).

As was observed for the patient dataset, the majority of the underlying diagnoses in the graft dataset were congenital anomalies of the urogenital tract (n=118; 55.4%), followed by glomerular disease (n=70; 32.9%) and other diagnoses (n=25; 11.7%) (Table 3.13).

Table 3.13: Demographic characteristics and aetiology of CKD for the graft dataset

Characteristic	**Graft data N=213**
Sex, n (%)	
Female	83 (39.0)
Male	130 (61.0)
Racial group, n (%)	
Black	114 (53.5)
White	73 (34.3)
Asian	13 (6.1)
Mixed race	13 (6.1)
Financial classification, n (%)	
Low SES [1]	13 (6.1)
Middle SES [2]	117 (54.9)
Private [3]	49 (23.0)
Foreign [4]	1 (0.5)
Unknown [5]	33 (15.5)
Diagnosis (individual), n (%)	
Dysplastic kidneys	32 (15.0)
PUV [6]	30 (14.1)
FSGS [7]	27 (12.7)
Congenital nephrotic syndrome	20 (9.4)
Primary reflux nephropathy	18 (8.5)
Other [8]	15 (7.0)
FSH [9]	20 (9.4)
RPGN [10]	14 (6.6)
ARPKD [11]	12 (5.6)
HUS [12]	7 (3.3)
VUR [13]	6 (2.8)
Glomerulonephritis	8 (3.8)
Lupus nephritis	3 (1.5)
APSGN [14]	1 (0.5)
Diagnosis (combined), n (%)	
Glomerular disease group [15]	70 (32.9)
Congenital group [16]	118 (55.4)
Other group [17]	25 (11.7)

[1] Low SES – patients on social pension, government grants (disability or social); [2] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [3] Private – patients on a medical aid, prisoner, suspect or road accident victims; [4] Foreign – foreign patients without documentation (illegally in South Africa); [5] Unknown – patients of unknown SES; [6] PUV – posterior urethral valves; [7] FSGS – focal segmental glomerulosclerosis; [8] Other - medullary cystic kidneys, Takayasu's arteritis, Lawrence Moon Biedl Syndrome, Henoch Schönlein Purpura, and primary hyperoxalosis; [9] FSH – focal segmental hyalinosis; [10] RPGN – rapidly progressive glomerulonephritis; [11] ARPKD – autosomal recessive polycystic kidney disease; [12] HUS – haemolytic uraemic syndrome; [13] VUR – vesico-ureteric reflux; [14] APSGN – acute post-streptococcal glomerulonephritis; [15] Glomerular disease group – made up of APSGN, FSGS, FSH, GN and RPGN; [16] Congenital disease group – ARPKD, congenital nephrotic syndrome, dysplastic kidneys, PUV, primary reflux nephropathy, and VUR; [17] Other – HUS, SLE, medullary cystic, Takayasu's arteritis, Lawrence Moon Biedl Syndrome, HSP, and primary hyperoxalosis.

3.3.3 Allograft details

Of the 213 grafts which were transplanted during the study period, one graft was received by the recipient in 141 (66.2%) cases, 48 (22.5%) recipients received a second graft, 20 (9.4%) recipients received a third transplant, and 4 (1.9%) recipients received a fourth graft. The following part of the analysis is restricted to the final graft received by the patient, in the study period. The median ages for the above groups were 12.4 years old (IQR: 9.2 to 14.7), 13.5 years (IQR: 12.0 to 16.2), 14.7 years (IQR: 12.0 to 16.2), and 16.9 years (IQR: 15.8 to 17.6), respectively. The overall median age for the 213 grafts received, was 13.3 years (IQR: 10.5 to 15.3); Table 3.14.

One hundred, sixty-five (77.5%) of the transplants occurred during the adolescent period, whereas 48 (22.5%) occurred outside of the adolescent period (in children <10 years of age).

One hundred, nineteen (55.9%) grafts were transplanted during the 1990's, and 94 (44.1%) were transplanted during the 2000's. With respect to the overall number of grafts received by the patient, in the group who had received one graft overall, 75 (53.2%) were transplanted during the 1990's, and 66 (46.8%) were during the 2000's. In the group that received two grafts in total, 30 (62.5%) transplants were performed during the 1990's, compared to 18 (37.5%) during the 2000's. In the group that received three grafts in total, 11 (55.0%) were during the 1990's, and 9 (45.0%) were in the 2000's. Most of the grafts transplanted in patients that received a total of four transplants (n=3; 75.0%) were done in the 1990's; Figure 3.21 and Table 3.14.

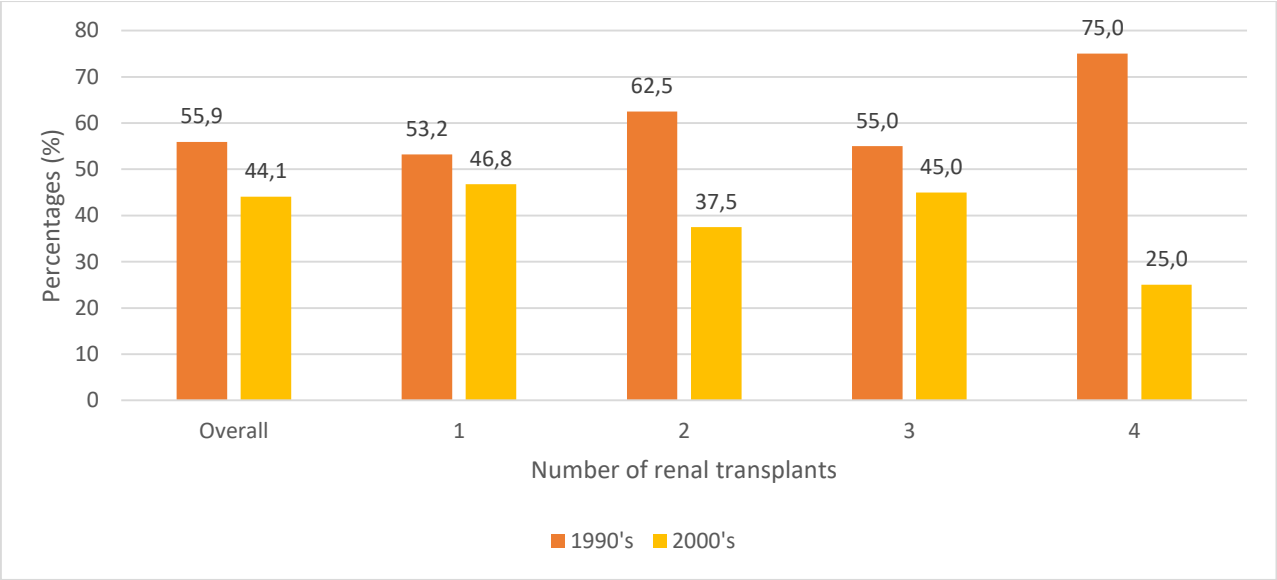


Figure 3.21: Bar graph showing the number of transplants in the *1990's versus the 2000's*

Of the 213 grafts transplanted in the 20-year period, 65 (30.5%) were from an RLD, and 148 (69.5%) were from a DD (Figure 3.22 and Table 3.14). With respect to the overall donor type of the 65 RLD grafts, 36 (55.4%) were from the patients' mothers, 21 (32.3%) were from fathers, 4 (6.1%) were from siblings, 2 (3.1%) were from aunts and 2 (3.1%) had an unknown RLD; Table 3.14.

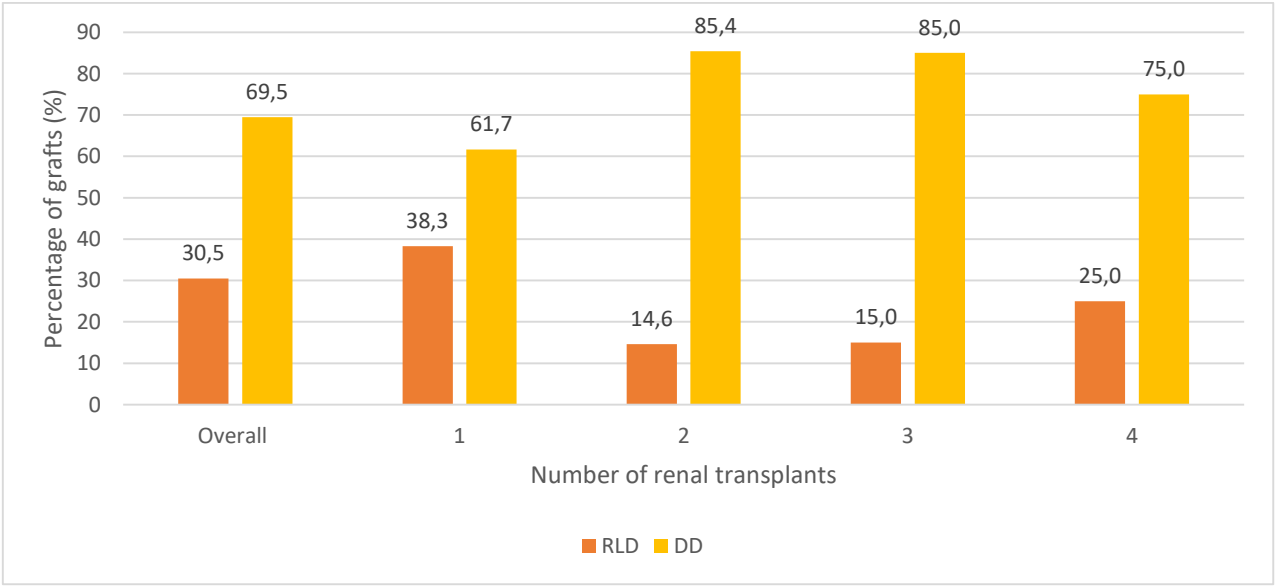


Figure 3.22: Distribution of the type of renal transplant received in the graft dataset in the study period

Immunosuppressive Regimen 1 was used in 123 (57.7%) of the 213 grafts, Regimen 2 was used in 73 (34.3%) grafts and 17 (8.0%) grafts where treated with Regimen 3. Of the 141 grafts where the recipient had had only one transplant, Regimen 1 was used in 74 (52.5%) of the grafts, Regimen 2 was used in 59 (41.8%) and Regimen 3 was used in 8 (5.7%). Among grafts received by patients that underwent two or three transplants (n=68), Regimen 1 was used in the majority of cases (n=47; 69.1%), Regimen 2 was used in 12 (17.6%) and Regimen 3 was used in 9 (13.2%); Figure 3.23 and Table 3.14.

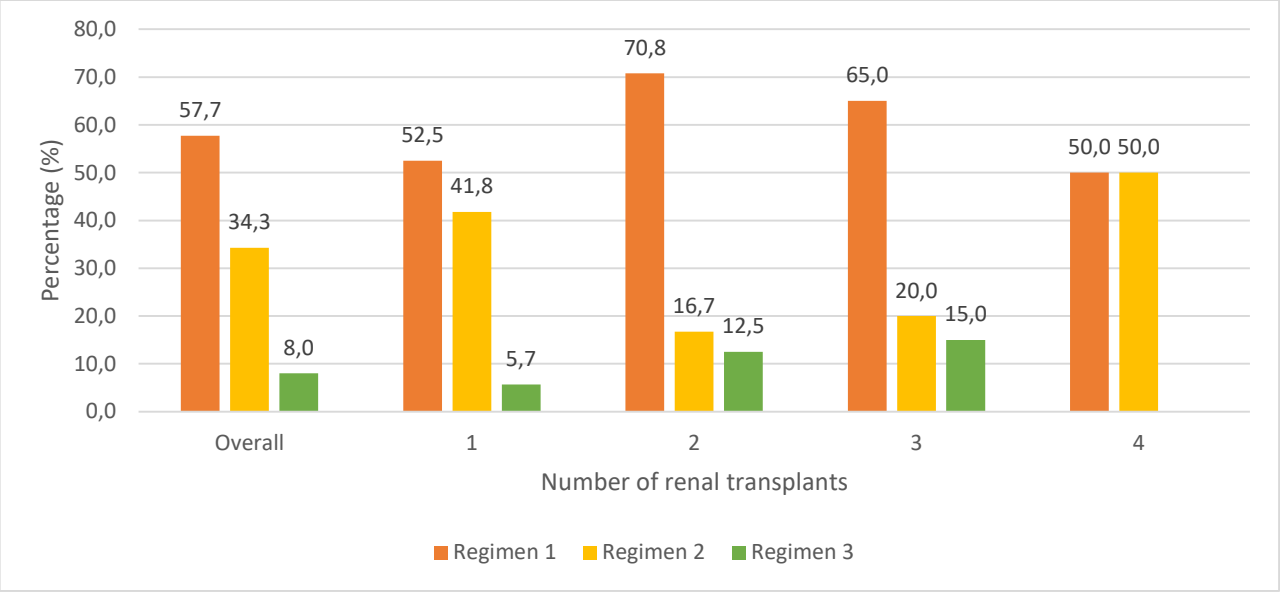


Figure 3.23: *Immunosuppressive regimen* per number of renal transplants

Of the group transplanted during the 1990's, immunosuppressive Regimen 1 was used in 109 (91.6%) grafts. Regimen 2 was the predominant immunosuppressive regimen in the 2000's, used in 69 (73.4%) grafts; Table 3.14.

Table 3.14: Details for the graft dataset in the study period – only final graft data are presented herein

Variable	Overall [1] (N=213) n (%)	Number of grafts received by patient during the study period [2]			
		One [3] n (%)	Two [4] n (%)	Three [5] n (%)	Four [6] n (%)
Patients, n (%)	213	141 (66.2)	48 (22.5)	20 (9.4)	4 (1.9)
Age (years), median (IQR)	13.3 (10.5, 15.3)	12.4 (9.2, 14.7)	13.5 (12.0, 16.2)	14.7 (12.0, 16.2)	16.9 (15.8, 17.6)
Decade transplanted, n (%)					
1990's	119 (55.9)	75 (53.2)	30 (62.5)	11 (55.0)	3 (75.0)
2000's	94 (44.1)	66 (46.8)	18 (37.5)	9 (45.0)	1 (25.0)
Type, n (%)					
RLD [7]	65 (30.5)	54 (38.3)	7 (14.6)	3 (15.0)	1 (25.0)
DD [8]	148 (69.5)	87 (61.7)	41 (85.4)	17 (85.0)	3 (75.0)
Donor, if RLD [9], n (%)					
Mother	36 (55.4)	30 (55.6)	4 (57.1)	1 (33.3)	1 (100.0)
Father	21 (32.2)	19 (35.2)	2 (28.6)	0 (0.0)	0 (0.0)
Sibling	4 (6.2)	3 (5.6)	0 (0.0)	1 (33.3)	0 (0.0)
Other	2 (3.1)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	2 (3.1)	0 (0.0)	1 (14.3)	1 (33.3)	0 (0.0)
Immunosuppressive regimen, n (%)	N=213	N=141	N=48	N=20	N=4
Regimen 1 [10]	123 (57.7)	74 (52.5)	34 (70.8)	13 (65.0)	2 (50.0)
Regimen 2 [11]	73 (34.3)	59 (41.8)	8 (16.7)	4 (20.0)	2 (50.0)
Regimen 3 [12]	17 (8.0)	8 (5.7)	6 (12.5)	3 (15.0)	0 (0.0)

[1] Overall – total number of patients receiving a renal transplant; [2] Total number of renal transplants received by patient (the final graft received by the recipient in the study period) – either one, two, three or four renal transplants overall; [3] One – 141/213 records available; [4] Two – 48/213 records available; [5] Three – 20/163 records available; [6] Four – 4/213 records available; [7] RLD – related living donor, 65/213 records available; [8] DD – deceased donor, 148/213 records available; [9] Donor, if RLD – 65/65 records; [10] Regimen 1 – Azathioprine/cyclosporine/prednisone; [11]Regimen 2 – Tacrolimus/mycophenolate mofetil (MMF)/prednisone; [12]Regimen 3 – Cyclosporine/MMF/prednisone.

3.3.4 Outcomes

3.3.4.1 Graft failure

Graft failure occurred in 149 (69.9%) of the 213 grafts. One hundred and ten (73.8%) grafts failed in the paediatric unit, and 39 (26.2%) failed in the adult unit. Graft failure occurred during the adolescent period (paediatric and adult unit combined) in 111 (74.5%) cases. Of these, 105 (94.6%) occurred in the paediatric unit, and 6 (5.4%) occurred in the adult unit; Figure 3.24.

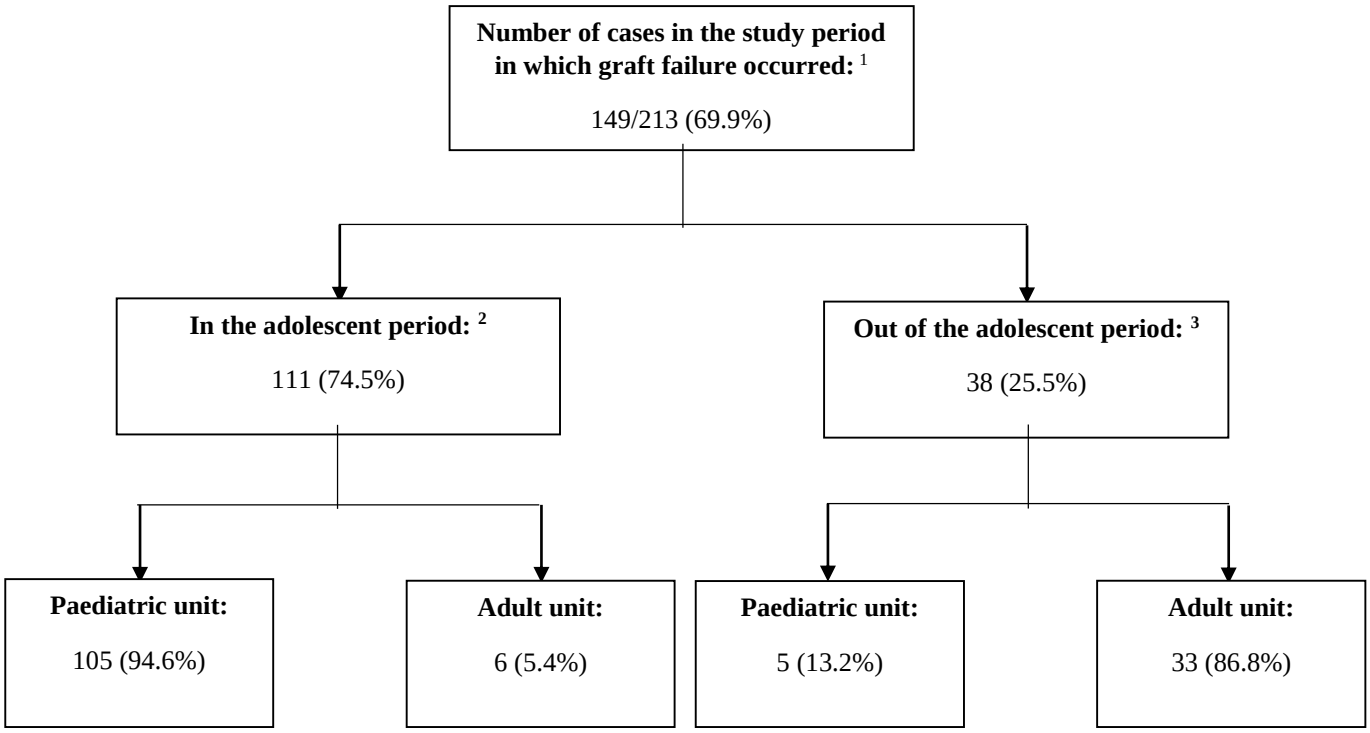


Figure 3.24: Graft failure analysis: Graft Dataset

[1] Number of graft failures. [2] Graft failure – occurred during the adolescent period – both paediatric and adult units.
[3] Graft failure – occurred outside of the adolescent period – both paediatric and adult units.

The median age at graft failure was 16.0 years (IQR: 13.8 to 19.0), and most of the graft failures (n=94; 63.1%) occurred in male patients. Furthermore, the majority of the patients in which graft failure occurred (n=92; 61.7%) were of black race. With respect to SES, the majority (n=82; 55.0%) of graft failures occurred in the middle SES group; Table 3.16.

Of the 111 grafts that failed in the adolescent period (10-19 years), the median age at graft failure was 14.9 years (IQR: 12.4 to 16.8). The youngest recipient was 10.0 years old, and the oldest was 18.9 years old. Most grafts failing in the adolescent period (n=105; 94.6%) were in the paediatric group, in which the median age was, 12.1 years (IQR: 10.2 to 13.9); the youngest patient was 1.9 years old, and the oldest was 18.7 years. The median age of the 6 (5.4%) patients in which graft

failure occurred in the adolescent period in the adult unit, was 18.2 years old (IQR: 17.7 to 18.9). The majority (n=69; 62.2%) of grafts failing in the adolescent period were from male patients. Similarly, the majority (n=71; 64.0%) of adolescent period graft failures occurred in black patients, and most (n=58; 55.2%) occurred in patients of middle SES; Table 3.16.

Graft rejection was the commonest cause of graft failure (n=60; 40.3%), followed by non-compliance (n=58; 38.9%), primary non-function (n=17; 11.4%), chronic allograft nephropathy (n=9; 6.0%), and recurrence of primary disease (n=4; 2.7%). There was 1 (0.7%) graft in which the cause of graft failure was distal ureteric obstruction resulting from intra-operative complications, followed by massive post-operative bleeding requiring nephrectomy (this cause was grouped as "Other"); Table 3.16.

Rejection was the commonest cause of graft failure in the adolescent period, occurring in 52 (46.9%) of the grafts, followed by non-compliance (n=28; 25.2%), and primary non-function (n=17; 15.3%). Chronic allograft nephropathy and recurrence of primary disease contributed to graft failure in 9 (8.1%), and 4 (3.6%) of the cases of graft failure occurring in the adolescent period, respectively. The most frequent cause of graft failure in the paediatric unit was rejection (n=51; 48.6%), whereas the most frequent cause of graft failure in the adult unit was non-compliance (n=5; 83.3%); Figure 3.25 and Table 3.16.

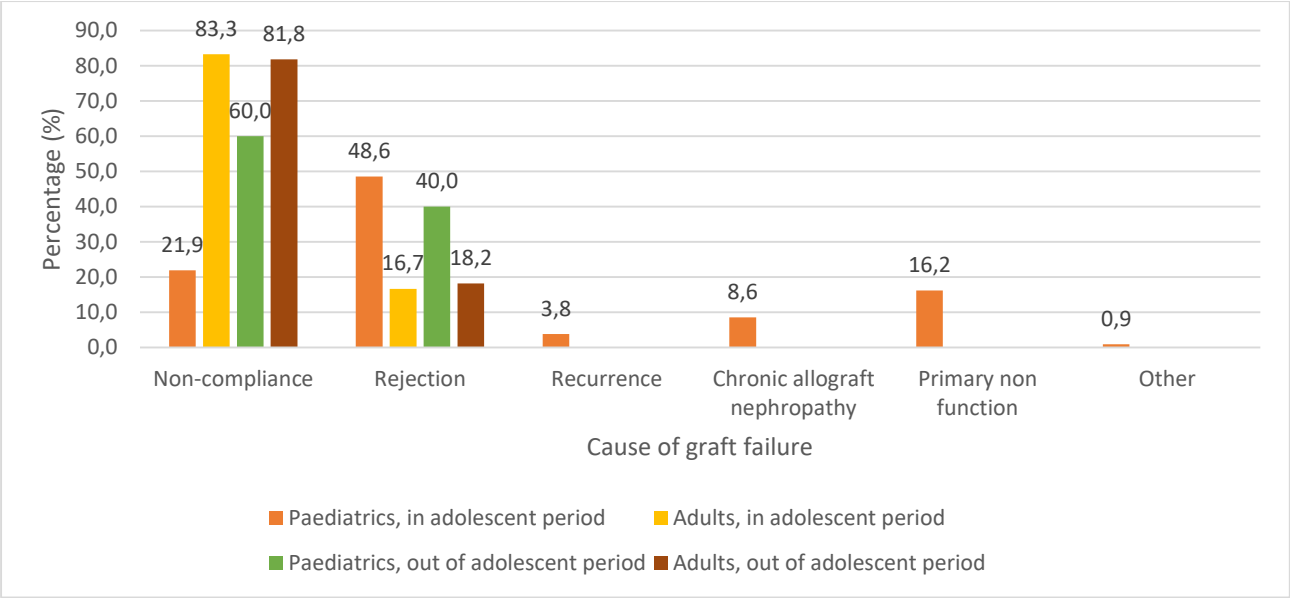


Figure 3.25: Distribution of the cause of graft failure in and out of the adolescent period, comparing paediatric and adult units for the graft data

Of the 149 cases in which graft failure occurred, 116 (77.9%) grafts were from a DD, and 33 (22.1%) were from an RLD. In the RLD category, the relationship of the donor to the patient was the mother in 18 (54.5%) of the cases, the father in 9 (27.3%), a sibling in 3 (9.1%) and an aunt in 1 (3.0%) case. The donor was unknown in 2 (6.1%) cases. Most 95 (63.8%) of the patients that experienced graft failure were on immunosuppressive Regimen 1 (Table 3.16).

Of the 111 grafts in which graft failure occurred during the adolescent period, 91 (82.0%) were from a DD, and 20 (18.0%) were from an RLD. The donors for the RLD grafts were the patients' mothers in 12 (60.0%), fathers in 5 (25.0%). In the majority (n=72; 64.9%) of the cases with graft failure in the adolescent period, immunosuppressive Regimen 1 was used; Table 3.16.

Table 3.15: Graft failure characteristics for the graft data in the study period

Variable	Overall N = 149	In adolescent period N = 111		Out of adolescent period N = 38	
		Paediatric	Adult	Paediatric	Adult
Patients, n (%)	-	105 (94.6)	6 (5.4)	5 (13.2)	33 (86.8)
Age (years), median (IQR)	16.0 (13.8, 19.0)	12.1 (10.2, 13.9)	18.2 (17.7, 18.9)	20.2 (19.7, 20.9)	21.7 (20.0, 25.2)
Sex, n (%)					
Female	55 (36.9)	40 (38.1)	2 (33.3)	1 (20.0)	12 (36.4)
Male	94 (63.1)	65 (61.9)	4 (66.7)	4 (80.0)	21 (63.6)
Race, n (%)					
Black	92 (61.7)	65 (61.9)	6 (100.0)	1 (20.0)	20 (60.6)
White	41 (27.5)	29 (27.6)	(0.0)	4 (80.0)	8 (24.3)
Asian	7 (4.7)	6 (5.7)	0 (0.0)	0 (0.0)	1 (3.0)
Mixed race	9 (6.1)	5 (4.8)	0 (0.0)	0 (0.0)	4 (12.1)
Financial classification, n (%)					
Low SES [1]	10 (6.7)	6 (5.7)	2 (33.3)	0 (0.0)	2 (6.1)
Middle SES [2]	82 (55.0)	58 (55.2)	4 (66.7)	1 (20.0)	19 (57.6)
Private [5]	31 (20.8)	21 (20.0)	0 (0.0)	3 (60.0)	7 (21.2)
Foreign [6]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown [7]	26 (17.5)	20 (19.1)	0 (0.0)	1 (20.0)	5 (15.1)
Immunosuppressive regimen, n (%)					
Regimen 1 [8]	95 (63.8)	71 (67.6)	1 (16.7)	3 (60.0)	20 (60.6)
Regimen 2 [9]	39 (26.2)	21 (20.0)	5 (83.3)	1 (20.0)	12 (36.4)
Regimen 3 [10]	15 (10.0)	13 (12.4)	0 (0.0)	1 (20.0)	1 (3.0)
Cause, n (%)					
Non-compliance	58 (38.9)	23 (21.9)	5 (83.3)	3 (60.0)	27 (81.8)
Rejection	60 (40.3)	51 (48.6)	1 (16.7)	2 (40.0)	6 (18.2)
Recurrence primary disease	4 (2.7)	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic allograft nephropathy	9 (6.0)	9 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)
Primary non-function	17 (11.4)	17 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other [11]	1 (0.7)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)

[1] Low SES – patients on social pension, government grants (disability or social); [2] Middle SES – individuals with an income of up to or equal to R72 000.00 per annum and households with an income up to or equal to R100 000.00 per annum; [3] Private – patients on a medical aid, prisoner, suspect or road accident victims; [4] Foreign – foreign patients without documentation (illegally in South Africa); [5] Unknown – patients of unknown SES; [6] Foreign – foreign patients without documentation (illegally in South Africa); [7] Unknown – patients of unknown SES; [8]Regimen 1 – Azathioprine/cyclosporine/prednisone; [9]Regimen 2 – Tacrolimus/mycophenolate mofetil (MMF)/prednisone; [10]Regimen 3 – Cyclosporine/MMF/prednisone; [11] Other – distal ureteric obstruction resulting from intra-operative complications, followed by massive bleeding post-operative requiring nephrectomy;

3.3.4.2 Non-compliance

Non-compliant episodes occurred in 52 (24.4%) of the grafts. In 18 (34.6%) grafts, non-compliance occurred once in the study period, while in 16 (30.8%) cases there were two episodes of non-compliance. In 8 (15.4%) cases, non-compliance occurred three times in the study, and in 10 (19.2%), non-compliance occurred four or more times (Table 3.17).

Most (n=31; 59.6%) of the non-complaint episodes occurred in males. In the majority of grafts in which non-compliance occurred, the patients were of black race (n=27; 51.9%), followed by white patients (n=20; 38.5%). The majority (n=31; 59.6%) of the non-compliant cases were of middle SES. The congenital disease group had the largest number of episodes of non-compliance (n=33; 63.5%), followed by the glomerular disease group (n=12; 23.1%), and the other group (n=7; 13.4%); Table 3.17.

Twenty-three (44.2%) of the non-compliant episodes occurred in patients transplanted in the 1990's, and 29 (55.8%) occurred in those transplanted in the 2000's. Patients transplanted during the adolescent period had the greatest number of episodes of non-compliance (n=37; 71.2%). In 38 (73.1%) cases, non-compliance occurred in the group of grafts in which one transplant occurred during the study period, compared to 14 (26.9%) cases in which there were two or more transplants which had occurred during the study period (Table 3.17).

Most (n=26; 50.0%) of the patients with non-compliance were on immunosuppressive Regimen 1, and 29 (55.8%) had DD grafts (Table 3.17).

Graft failure during the adolescent period occurred in 16 (30.8%) of the non-compliant cases, followed by 5 (9.6%) cases in which the patient was eventually transferred to another facility. In 2 (3.9%) cases, the patient was lost to follow up and death occurred in 1 (1.9%) case. In 5 (9.6%) of the non-compliant cases, the patient was eventually transferred to another facility, (Table 3.17). Twenty-eight (53.8%) of the patients that were non-compliant had preserved graft function at the end of the study (Table 3.17).

Table 3.16: Non-compliant episodes, for the graft data

Characteristic	Paediatric data N=33	Adult data N=19	Combined paediatric and adult data N=52
Number of episodes of non-compliance			
1	12 (36.4)	6 (31.6)	18 (34.6)
2	10 (30.3)	6 (31.6)	16 (30.8)
3	5 (15.1)	3 (15.8)	8 (15.4)
≥4	6 (18.2)	4 (21.0)	10 (19.2)
Sex, n (%)			
Female	13 (39.4)	8 (42.1)	21 (40.4)
Male	20 (60.6)	11 (57.9)	31 (59.6)
Racial group, n (%)			
Black	14 (42.4)	13 (68.4)	27 (51.9)
White	17 (51.5)	3 (15.8)	20 (38.5)
Asian	0 (0.0)	1 (5.3)	1 (1.9)
Mixed race	2 (6.1)	2 (10.5)	4 (7.7)
Financial classification, n (%)			
Low SES	2 (6.1)	2 (10.5)	4 (7.7)
Middle SES	18 (54.5)	13 (68.4)	31 (59.6)
Private	9 (27.3)	3 (15.8)	12 (23.1)
Foreign	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	4 (12.1)	1 (5.3)	5 (9.6)
Diagnosis (combined), n (%)[17]			
Glomerular disease group [1]	22 (66.7)	11 (57.9)	33 (63.5)
Congenital group [2]	6 (18.2)	6 (31.6)	12 (23.1)
Other group [3]	5 (15.1)	2 (10.5)	7 (13.4)
Transplanted during the adolescent period, n (%)			
Yes	23 (69.7)	14 (73.7)	37 (71.2)
No	10 (30.3)	5 (26.3)	15 (28.8)
Decade transplanted during, n (%)			
1990's	16 (48.5)	7 (36.8)	23 (44.2)
2000's	17 (51.5)	12 (63.2)	29 (55.8)
Total number of renal transplants, during the study period, n (%)			
1	22 (66.7)	16 (84.2)	38 (73.1)
≥2	11 (33.3)	3 (15.8)	14 (26.9)
Immunosuppressive regimen, n (%)			
Regimen 1 (A/C/P) [4]	18 (54.5)	8 (42.1)	26 (50.0)
Regimen 2 (T/M/P) [5]	12 (36.4)	10 (52.6)	22 (42.3)
Regimen 3 (C/M/P) [6]	3 (9.1)	1 (5.3)	4 (7.7)
Type of renal transplant, n (%)			
RLD [7]	11 (33.3)	12 (63.3)	23 (44.2)
DD [8]	22 (66.7)	7 (36.7)	29 (55.8)
Donor, if RLD [9], n (%)			
Mother	6 (54.5)	7 (58.3)	13 (56.5)
Father	3 (27.3)	5 (41.7)	8 (34.8)
Sibling	2 (18.2)	0 (0.0)	2 (8.7)
Aunt	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Final outcome of the patients, during the adolescent period, n (%)			
Graft failure	15 (45.4)	1 (5.3)	16 (30.8)
Death	0 (0.0)	1 (5.3)	1 (1.9)
Transfer to another facility	2 (6.1)	3 (15.8)	5 (9.6)
Lost to follow up	0 (0.0)	2 (10.4)	2 (3.9)
Preserved graft function	16 (48.5)	12 (63.2)	28 (53.8)

[1]Glomerular disease group – APSGN, FSGS, FSH, GN and RPGN; [2]Congenital disease group – ARPKD, congenital nephrotic syndrome, dysplastic kidneys, PUV, primary reflux nephropathy, and VUR; [3]Other – HUS, SLE, medullary cystic, Takayasu's arteritis, Lawrence Moon Body Biedl, HSP, and primary hyperoxalosis; [4]Regimen 1 – A/C/P – Azathioprine, cyclosporine, prednisone; [5]Regimen 2 – T/M/P – Tacrolimus, MMF, prednisone; [6]Regimen 3 – C/M/P – Cyclosporine, MMF, prednisone; [7]RLD – related living donor; [8]DD – deceased donor; [9]Donor, if RLD; [10]Preserved graft function - patients had a functioning graft at the conclusion of the study period.

3.3.4.3 Rejection episodes and renal biopsies

A total of 133 rejection episodes occurred in the study period for the graft dataset. In 74 (55.6%) of the cases, one rejection episode occurred in the study period, 31 (23.4%) had two episodes, 14 (10.5%) had three, and 14 (10.5%) had four or more episodes (Table 3.18).

The median age of patients with one rejection episode was 14.7 years (IQR: 12.7 to 16.2), for those in which two rejection episodes occurred, the median age was also 14.7 years (IQR: 12.2 to 15.6). For those cases in which there were three and four rejection episodes, the median age was 14.0 years (IQR: 11.8 to 15.9) and 15.0 years (IQR: 13.5 to 16.2), respectively. The median number of days from the date of transplant to the date of rejection episode was 620 days (IQR: 310 to 1312), 937 days (IQR: 574, 1499), 1305 days (IQR: 795 to 2382), and 1610 days (IQR: 1118 to 2306), for one, two, three and four or more rejection episodes respectively (Table 3.18).

Table 3.17: Rejection episodes in the graft dataset (paediatric unit)

Variable	Number of rejection episodes during the adolescent period N=133			
	1	**2**	**3**	**≥4**
Number of patients, n (%)	74 (55.6)	31 (23.4)	14 (10.5)	14 (10.5)
Age (years), median (IQR)	14.7 (12.7, 16.2)	14.7 (12.2, 15.6)	14.0 (11.8, 15.9)	15.0 (13.5, 16.2)
Number of days from transplant to date of rejection episode, median (IQR) [1]	620 (310, 1312)	937 (574, 1499)	1305 (795, 2382)	1610 (1118, 2306)
Sex, n (%)				
Female	35 (47.3)	12 (38.7)	4 (28.6)	2 (14.3)
Male	39 (52.7)	19 (61.3)	10 (71.4)	12 (85.7)
Race, n (%)				
Black	39 (52.7)	15 (48.4)	9 (64.3)	9 (64.3)
White	29 (39.2)	13 (41.9)	5 (35.7)	5 (35.7)
Asian	2 (2.7)	1 (3.2)	0 (0.0)	0 (0.0)
Mixed race	4 (5.4)	2 (6.5)	0 (0.0)	0 (0.0)
Type of transplant, n (%)				
RLD	29 (39.2)	13 (41.9)	5 (35.7)	4 (28.6)
DD	45 (60.8)	18 (59.1)	9 (64.3)	10 (71.4)
Immunosuppressive regimen, n (%)				
Regimen 1 [2]	32 (43.2)	11 (35.5)	3 (21.4)	3 (21.4)
Regimen 2 [3]	32 (43.2)	16 (51.6)	9 (64.3)	8 (57.2)
Regimen 3 [4]	10 (13.6)	4 (12.9)	2 (14.3)	3 (21.4)
Non-compliance, n (%)				
Yes	30 (40.5)	20 (64.5)	10 (71.4)	0 (0.0)
No	44 (59.5)	11 (35.5)	4 (28.6)	14 (100.0)

[1]Number of days from transplant to rejection episode – calculated from the date of transplant to date of rejection episode; [2]Regimen 1 – Azathioprine, cyclosporine, prednisone; [3]Regimen 2 – Tacrolimus, mycophenolate mofetil (MMF), prednisone; [4]Regimen 3 – Cyclosporine, MMF, prednisone.

A total of 46 (59.7%) renal biopsies were performed on the 77 grafts in which rejection episodes occurred during follow-up in the paediatric unit in the adolescent period. In 40 (87.0%) cases, one renal biopsy was performed, and in 6 (13.0%) two biopsies were performed during the adolescent period. The median age at which the first biopsy was performed at was, 14.9 years (IQR: 12.4 to 16.5), and the median age at second biopsy was 16.0 years (IQR: 15.4 to 17.8). The first biopsy was

performed at a median of 353 days (IQR: 51 to 1118) post-transplant, and the second biopsy was performed at a median of 964 days (IQR: 589 to 1589) thereafter.

Histological findings at first biopsy included acute cell mediated rejection in 21 (52.5%) of cases, antibody mediated rejection in 7 (17.5%), 4 (10.0%) with CNI toxicity, and 4 (10.0%) with both antibody- and cell mediated rejection. For 3 (7.5%) of the renal biopsies, the finding was "other" – ATN, chronic allograft nephropathy and vascular infarct. There was 1 (2.5%) case, where the biopsy finding was recurrence of primary disease (FSGS). The most frequent finding for the second renal biopsy (n=6) was acute cell mediated rejection, in 2 cases. Antibody mediated rejection, CNI toxicity, and both cell mediated and antibody mediated rejection each accounted for 1 case. There was 1 (16.7%) case in which a suboptimal biopsy specimen failed to identify the cause of the rejection; Figure 3.26.

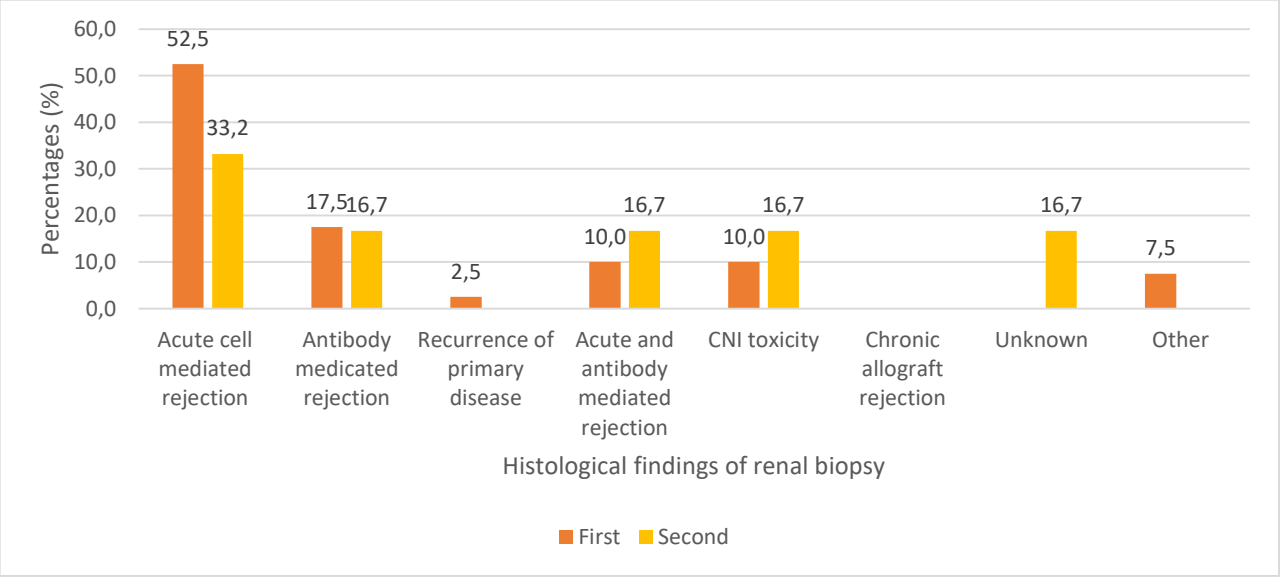


Figure 3.26: *Histological findings* of renal biopsies performed

3.3.5 Survival analysis

The overall 1-year, 3-year, 5-year, and 10-year graft survival amongst the whole study group was 85.9%, 67.6%, 56.8%, and 40.4% respectively. The 1-year, 3-year, 5-year, and 10-year graft survival in the group of patients transplanted during the adolescent period, was 86.5%, 63.5%, 51.4%, and 34.5% respectively. This was poorer than the group of patients transplanted prior to the adolescent period that subsequently entered adolescence with a functioning graft, who had much better 1-year, 3-year, 5-year, and 10-year graft survival, at 100.0%, 97.1%, 94.1%, and 94.1% respectively.

Table 3.18: Graft survival estimates

	Overall (%)	Transplant during adolescence (%)	Transplant prior to adolescence, entered adolescence with functioning graft (%)
1-year	85.9	86.5	100.0
3-year	67.6	63.5	97.1
5-year	56.8	51.4	94.1
10-year	40.4	34.5	94.1

Of the 213 grafts in the graft dataset, graft failure occurred during the adolescent period in 111 (52.1%) grafts during the study period. The median time to graft failure was 1808 days (95% Confidence Limit (CL), 1402-2124 days), Figure 3.27.

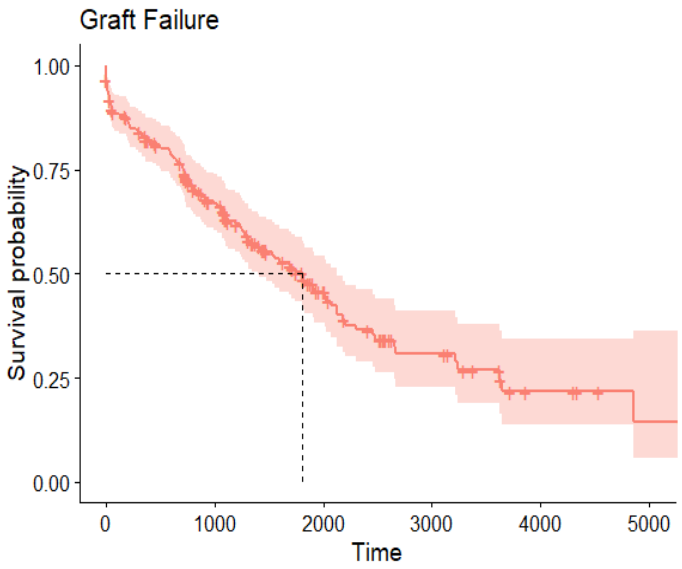


Figure 3.27: Kaplan-Meier curve of the *unstratified graft survival analysis* with median time to graft failure.

In univariate analyses of demographic characteristics, median time to graft failure was similar in males (1906 days; 95% CL: 1233 to 2454 days), and females (1594 days; 95% CL: 1340 to 2654 days) (p-value=0.72). When stratifying by race there was significantly better graft survival in the white patient group (2654 days; 95% CL: 2018 to NA days), compared to the non-white group of patients (1311 days; 95% CL: 1091 to 1813 days) (p-value<0.001). SES did not contribute significantly to graft survival (p-value=0.21); Figure 3.28 and Table 3.19.

Graft survival was significantly better in patients in the congenital diagnosis group (1914 days; 95% CL: 1553 to 2668 days), followed by the other diagnosis group (1830 days; 95% CL: 1813 to NA days), compared to the glomerular disease group (1091 days; 95% CL: 728 to 2120 days) (p-value=0.019). Further stratification of graft survival by the glomerular disease group, compared to the other diagnosis group (comprising the congenital group, and the other diagnosis group), revealed significantly better graft survival in the 'other' group (2018 days; 95% CL: 1682 to 2668)

compared to the glomerular group (1091 days; 95% CL: 728 to 2120 days) (p-value=0.003); Figure 3.28 and Table 3.19.

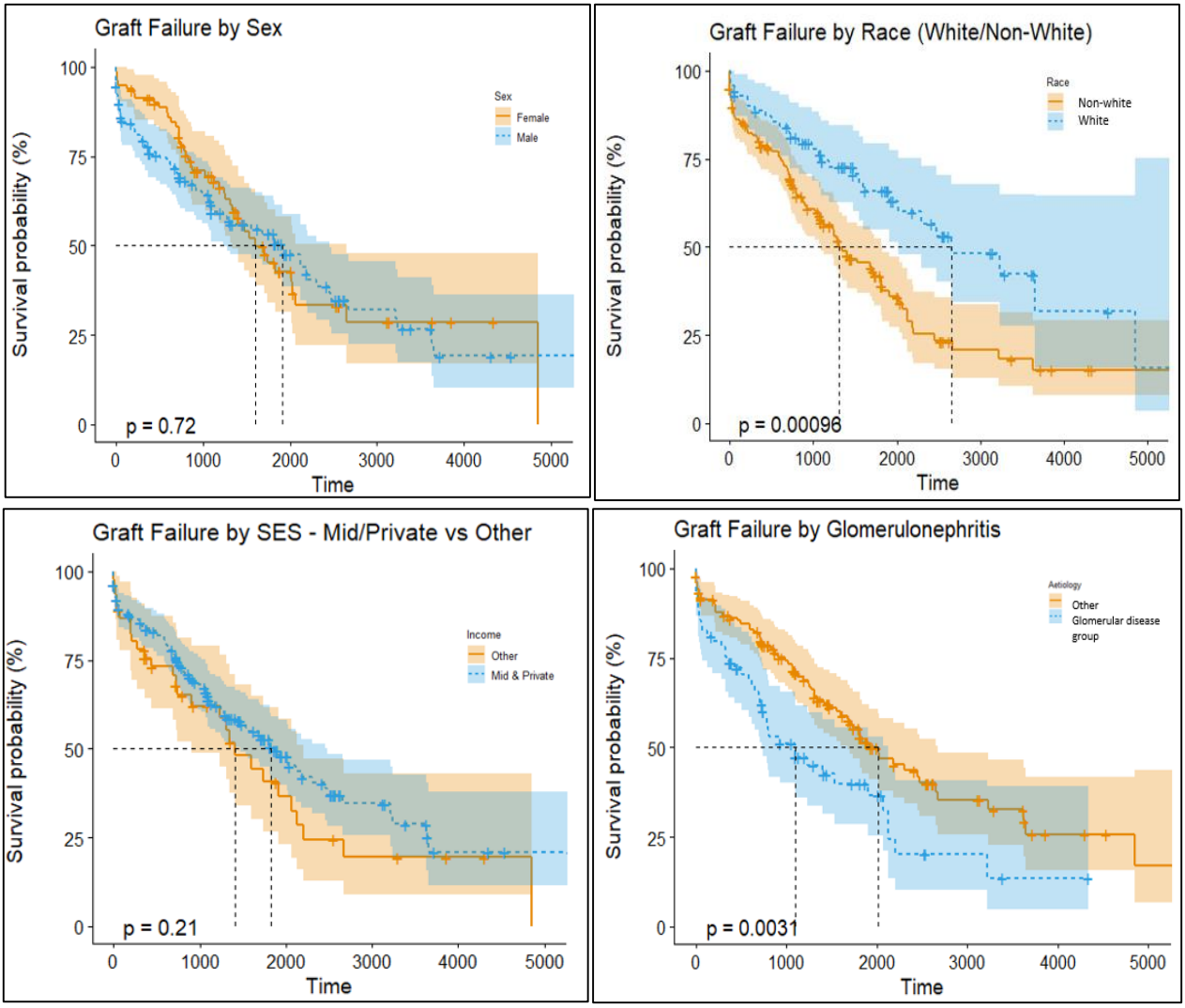


Figure 3.28: Kaplan-Meier curves showing graft survival by *patient sex, race, SES, and diagnosis*

In univariate analysis of transplant characteristics, graft survival was significantly longer in children who received immunosuppressive Regimen 2 (2475 days; 95% CL: 1830 to NA days), compared to those who received Regimen 1 (1311 days; 95% CL: 984 to 2064 days), or Regimen 3 (1091 days; 95% CL: 293 to NA days) (p-value=0.002). Graft survival was significantly better in the group of patients who were transplanted during the 2000's (2124 days; 95% CL: 1808 to NA days), compared to those transplanted in the 1990's (1252 days; 95% CL: 984 to 2024 days) (p-value=0.002); Figure 3.29 and Table 3.19.

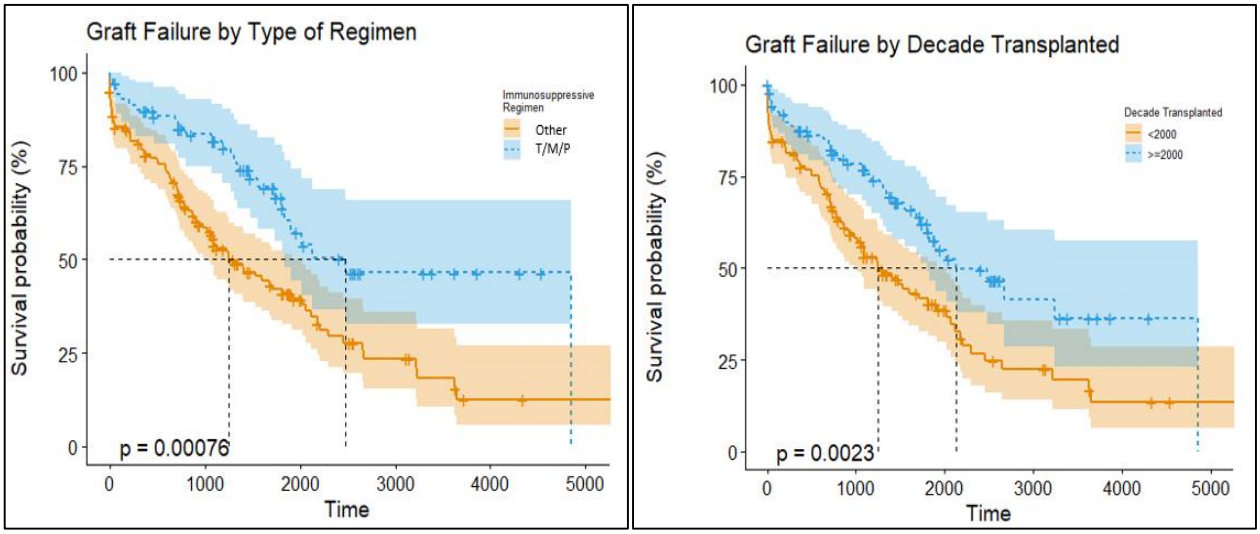


Figure 3.29: Kaplan-Meier curves showing graft survival by type of *immunosuppressive regimen and decade transplanted*

Graft survival was also significantly better in patients transplanted prior to entering the adolescent period (3218 days; 95% CL: 2120 to NA days), compared to those that were transplanted during the adolescent period (1409 days; 95% CL: 1091 to 1914 days) (p-value<0.001) (Figure 3.30 and Table 3.19).

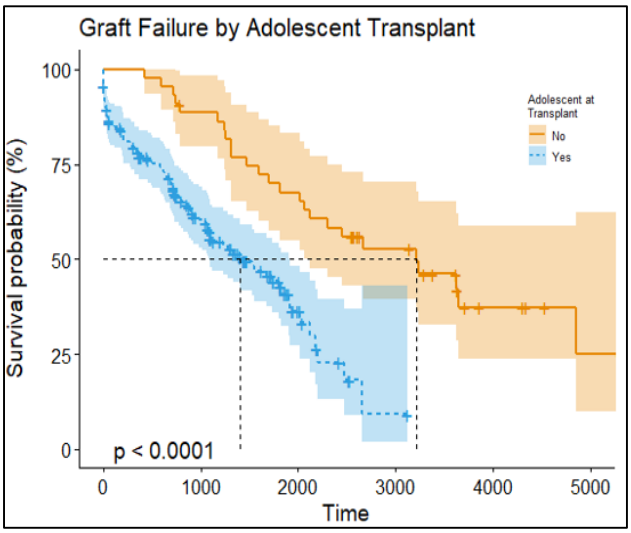


Figure 3.30: Kaplan-Meier curve showing graft survival by *transplant prior to the adolescent period*

Grafts obtained from RLD had significantly longer survival times (3235 days; 95% CL: 2654 to NA days), compared to those from DD (1311 days; 95% CL: 1071 to 1813 days) (p-value<0.001). However, graft survival was similar regardless of the relationship of the RLD donor to the recipient (p-value=0.46); Figure 3.31 and Table 3.19.

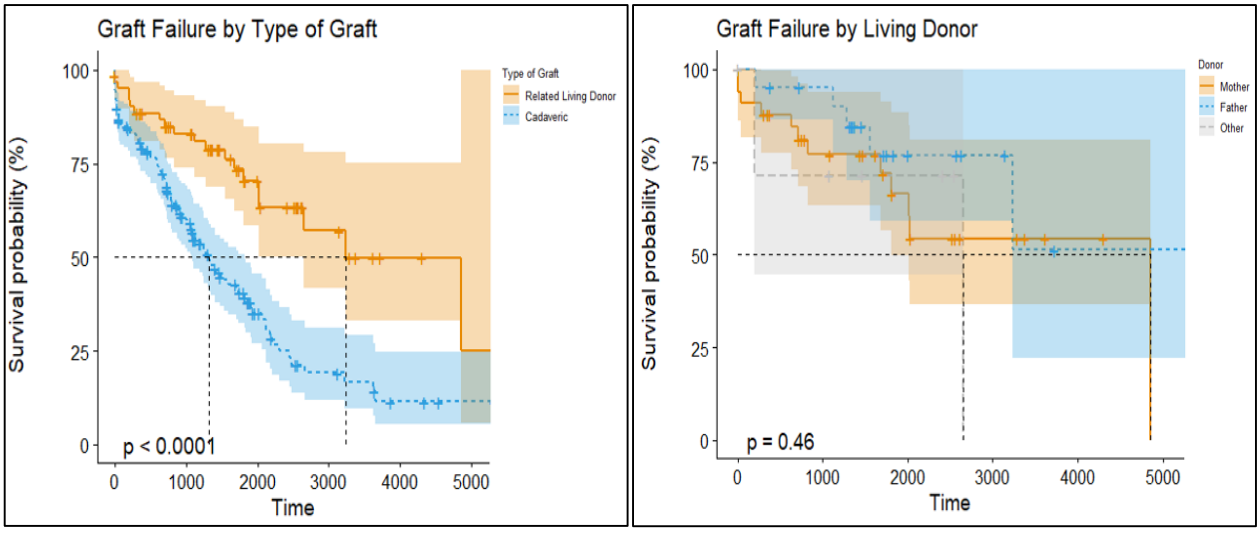


Figure 3.31: Kaplan-Meier curves showing graft survival by *type of graft and by living donor relation*

Patients who received one renal transplant in total had significantly longer graft survival (2120 days; 95% CL: 1813 to 3218 days) than did those with two or more renal transplants during the study period (1021 days; 95% CL: 781 to 1682 days) (p-value<0.001); Figure 3.32 and Table 3.19.

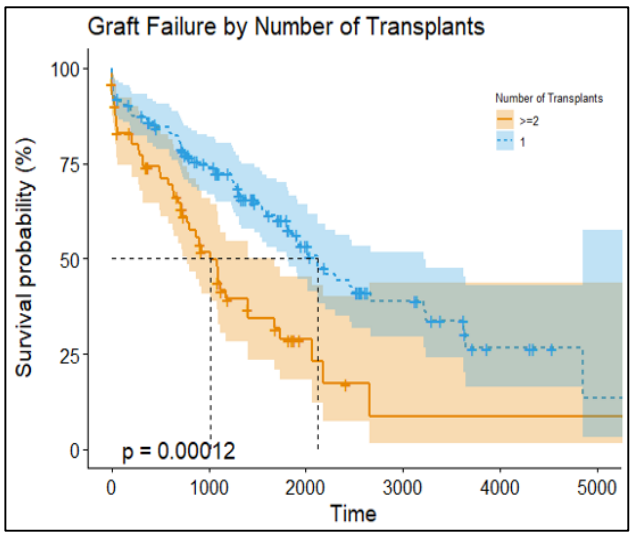


Figure 3.32: Kaplan-Meier curve showing graft survival by *number of renal transplants*

Patients transferred to the adult nephrology unit, had significantly increased graft survival (with no estimate for median graft survival amongst those transferred to the adult nephrology unit) compared to a median graft survival time of 1245 days (95% CI: 984 to 1594 days) in children not transferred to the adult service. Graft failure occurred in 6 out of the 52 patients (11.5%) transferred across, compared to 105 out of 157 patients (66.9%) who remained in the paediatric nephrology unit (p-value<0.001); Figure 3.33 and Table 3.19.

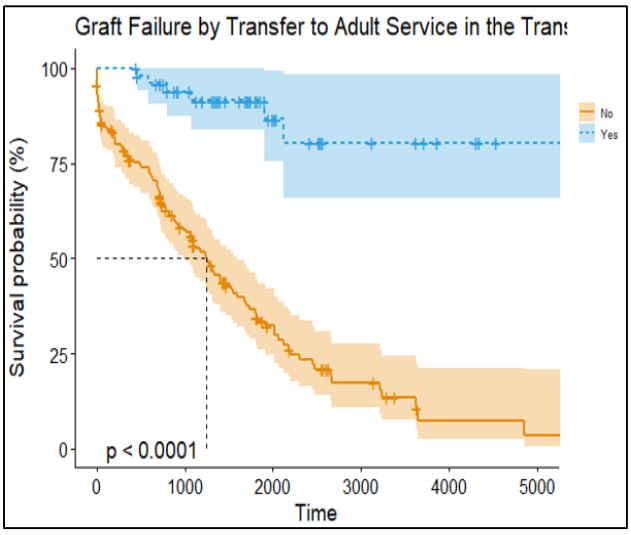


Figure 3.33: Kaplan-Meier curve showing graft survival by patients *transferred to the adult service*

Baseline eGFR did not impact on graft survival (p-value=0.83); however graft survival times were impacted by the final measured eGFR, with significantly better survival times in those grafts in which the final measured eGFR was ≥10 mL/min/1.73m^2 (2120 days; 95% CL: 1813 to 3218 days) compared to those grafts in which the final measured eGFR was <10 mL/min/1.73m^2 (212 days; 95% CL: 52 to 740 days) (p-value <0.001); Figure 3.34 and Table 3.19.

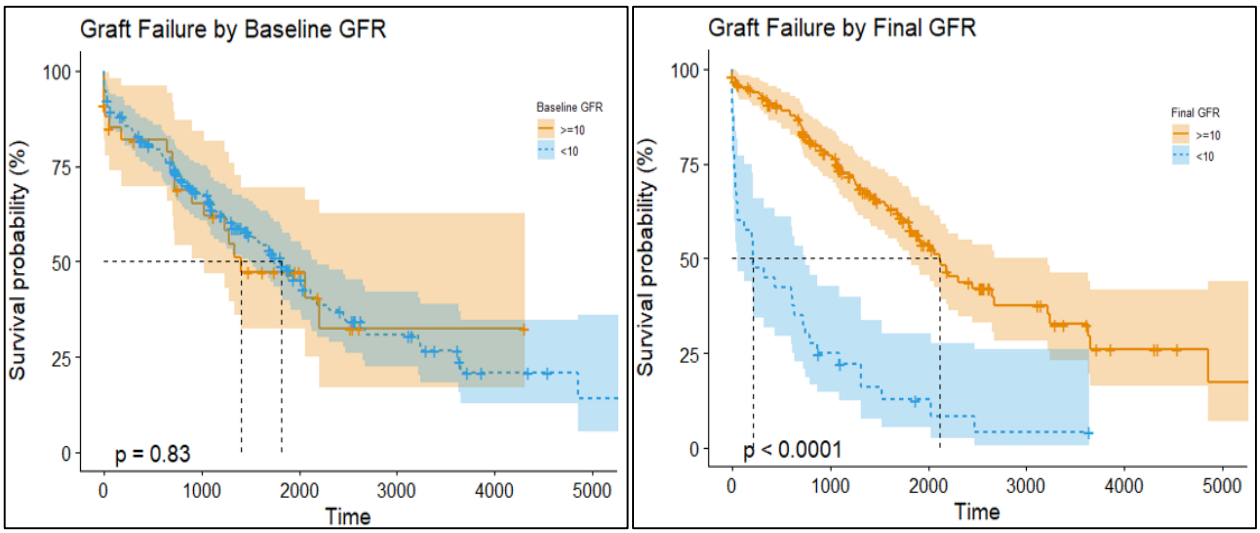


Figure 3.34: Kaplan-Meier curves showing graft survival by *eGFR values*

Patients who were compliant with their follow up, were shown to have superior graft survival (with no estimate for median graft survival), compared to those patients who were ever non-compliant (1340 days; 95% CL: 1096 to 1813 days) (p-value<0.0001); Figure 3.35 and Table 3.19.

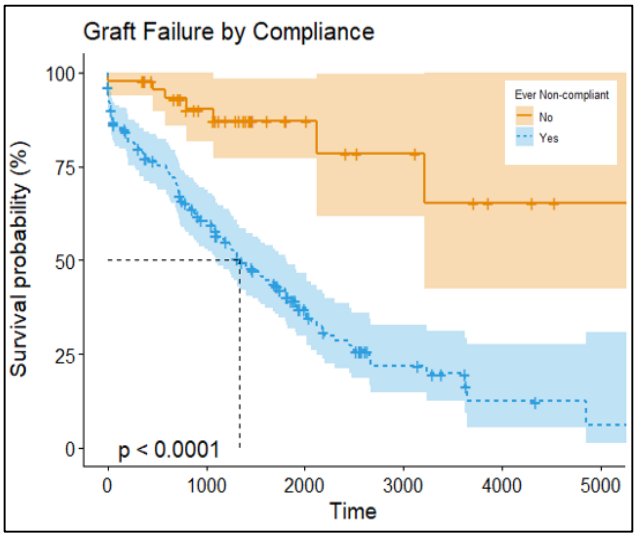


Figure 3.35: Kaplan-Meier curves showing graft survival by *compliance*

Rejection episodes, either prior to entering adolescence (p-value=0.58) or during the adolescent period (p-value=0.9) did not impact on graft survival; Figure 3.36 and Table 3.19.

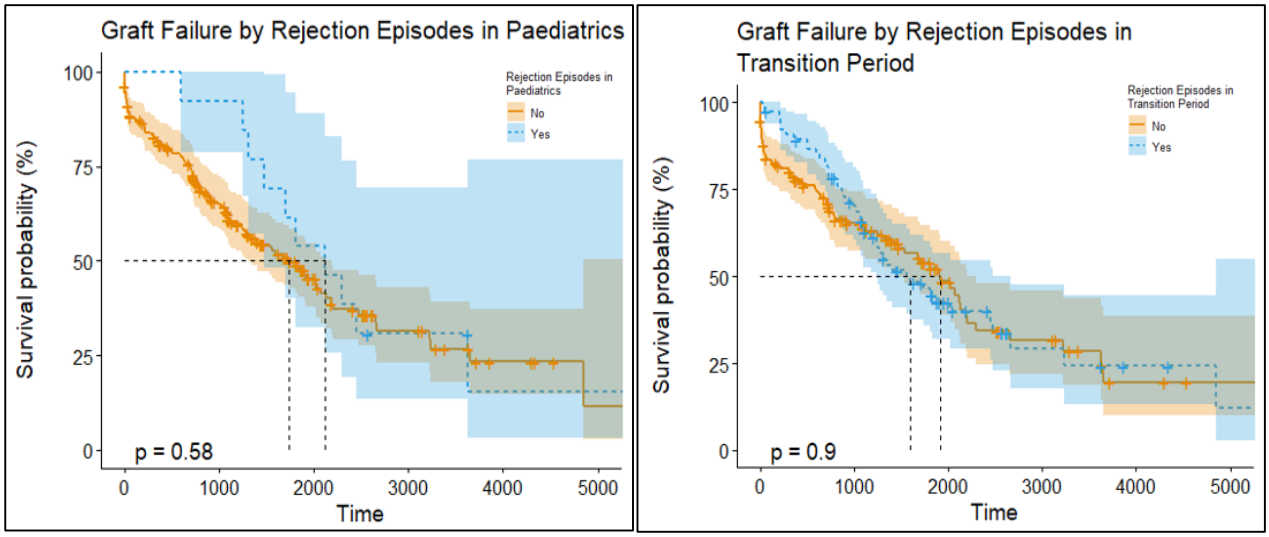


Figure 3.36: Kaplan-Meier curves showing graft survival by *rejection episodes*

Table 3.19: Univariate analysis constructed from Cox Proportional Hazards modelling: Graft Survival

Variable	Graft failure N=111 n (%)	Graft survival N=102 n (%)	HR (95% CL of HR) [1]	*P* value [2]
Sex				
Male	69 (62.2)	61 (59.8)	1.1 (0.7 – 1.6)	0.714
Female	42 (37.8)	41 (40.2)	Ref.	
Race				
White	29 (26.1)	44 (43.1)	0.5 (0.3 – 0.8)	0.001
Non-white	82 (73.9)	58 (56.9)	Ref.	
Financial classification				
Middle income or private	83 (74.8)	83 (81.4)	0.8 (0.5 – 1.2)	0.216
Other SES groups	28 (25.2)	19 (18.6)	Ref.	
Diagnosis				
Glomerulonephritis group	42 (37.8)	28 (27.5)	1.8 (1.2 – 2.6)	0.004
Other diagnoses, combined	69 (62.2)	74 (72.5)	Ref.	
Immunosuppressive regimen (T/M/P)				
T/M/P (Regimen 2) [3]	26 (23.4)	47 (46.1)	0.5 (0.3 – 0.7)	0.001
Regimens 1 and 3 [4]	85 (76.6)	55 (53.9)	Ref.	
Transplanted during adolescent period				
Yes	86 (77.5)	79 (77.4)	2.9 (1.7 – 5.0)	<0.001
No	25 (22.5)	23 (22.6)	Ref.	
Decade transplanted				
2000's	86 (77.5)	23 (22.6)	0.5 (0.4 – 0.8)	0.003
1990's	25 (22.5)	79 (77.4)	Ref.	
Type of renal transplant				
DD [5]	91 (82.0)	57 (55.9)	2.7 (1.7 – 4.5)	<0.001
RLD [6]	20 (18.0)	45 (44.1)	Ref.	
Number of transplants in study period				
<2	67 (60.4)	74 (72.5)	0.5 (0.3 – 0.7)	<0.001
≥2	44 (39.6)	28 (27.5)	Ref.	
Transfer to adult unit				
Yes	6 (5.4)	48 (47.1)	0.1 (0.04 – 0.2)	<0.001
No	105 (94.6)	54 (52.9)	Ref.	
eGFR values [7]				
At time of transplant (eGFR < 10)	-	-	0.9 (0.6 – 1.6)	0.822
Final eGFR taken during study period (eGFR < 10)	-	-	4.5 (3 – 6.7)	<0.001
Ever non-compliant paediatrics				
Yes	39 (35.1)	27 (26.5)	5.2 (2.4 – 11.0)	<0.001
No	72 (64.9)	75 (73.5)	Ref.	
Rejection episodes prior to adolescent period				
Yes	10 (9.0)	3 (2.9)	0.8 (0.4 – 1.6)	0.580
No	101 (91.0)	99 (97.1)	Ref.	
Rejection episodes in the adolescent period				
Yes	45 (40.5)	32 (31.4)	1.0 (0.7 – 1.4)	0.891
No	66 (59.5)	70 (68.6)	Ref.	

[1]Univariate analysis – HR (95% CL of HR) - calculated hazards ratio with 95% confidence limit using Cox proportional hazards analysis (adjusted for transfer to another facility and LTFU); [2]*P* value – using Log rank test and Kaplan-Meier Curve, *P* value <0.05 considered statistically significant; [3]T/M/P (Regimen 2) – Tacrolimus, mycophenolate mofotil (MMF), prednisone; [4]A/C/P (Regimen 1) – Azathioprine, cyclosporine, prednisone; C/M/P (Regimen 3) – Cyclosporine, MMF, prednisone [5]DD – Deceased donor; [6]RLD – related living donor; [7]eGFR – estimated glomerular filtration rates. Ref. = referent.

In multivariate analysis, race was the only demographic factor that contributed significantly to graft survival, with white patients having significantly better survival, compared to the patients in the non-white group (p-value=0.005). Neither SES (p-value=0.411) nor the primary renal diagnosis (p-value=0.148) were found not to contribute significantly to graft survival; Table 3.20. Transplant characteristics that were significantly associated with graft survival in the multivariable model included transplant prior to the adolescent period (p-value<0.001), compliance in terms of follow-up at the nephrology unit (p=0.012), and receipt of a RLD transplant (p=0.047). Furthermore, transfer to the adult service contributed significantly to graft survival (p-value<0.001) (AIC 897.2; p-value<0.001); Table 3.20.

Table 3.20: Multivariate analysis for graft survival

Variable	Graft failure N=111 n (%)	Graft survival N=102 n (%)	HR (95% CL of HR) [1]	*P* value [2]
Race				
White	29 (26.1)	44 (43.1)	0.5 (0.3 – 0.8)	0.005
Non-white	82 (73.9)	58 (56.9)	Ref.	
Financial classification				
Middle SES or private	83 (74.8)	83 (81.4)	0.8 (0.5 – 1.3)	0.411
Other SES groups	28 (25.2)	19 (18.6)	Ref.	
Diagnosis				
Glomerulonephritis group	42 (37.8)	28 (27.5)	1.4 (0.9 – 2.2)	0.148
Other diagnoses, combined	69 (62.2)	74 (72.5)	Ref.	
Immunosuppressive regimen (T/M/P)				
T/M/P (regimen 2) [3]	26 (23.4)	47 (46.1)	0.9 (0.5 – 1.8)	0.846
Regimens 1 and 3 [4]	85 (76.6)	55 (53.9)	Ref.	
Transplanted during adolescent period				
Yes	86 (77.5)	79 (77.4)	3.2 (1.8 – 5.5)	<0.001
No	25 (22.5)	23 (22.6)	Ref.	
Decade transplanted				
2000's	86 (77.5)	23 (22.6)	0.9 (0.5 – 1.7)	0.813
1990's	25 (22.5)	79 (77.4)	Ref.	
Type of renal transplant				
DD [5]	91 (82.0)	57 (55.9)	1.7 (1.0 – 2.9)	0.047
RLD [6]	20 (18.0)	45 (44.1)	Ref.	
Number of transplants in study period				
<2	67 (60.4)	74 (72.5)	0.8 (0.5 – 1.2)	0.257
≥2	44 (39.6)	28 (27.5)	Ref.	
Transfer to the adult unit				
Yes	6 (5.4)	48 (47.1)	0.1 (0.1 – 0.3)	<0.001
No	105 (94.6)	54 (52.9)	Ref.	
Ever non-compliant paediatrics				
Yes	39 (35.1)	27 (26.5)	2.8 (1.3 – 6.3)	0.012
No	72 (64.9)	75 (73.5)	Ref.	
eGFR values [7]				
Final eGFR taken during study period (eGFR <10)	-	-	2.9 (1.9 – 4.5)	<0.001

[1]Multivariate analysis – HR (95% CL of HR) - calculated hazards ratio with 95% confidence limit using Cox proportional hazards analysis (adjusted for transfer to another facility and LTFU); [2]*P* value – using Log rank test and Kaplan-Meier Curve; [3]T/M/P (Regimen 2) – Tacrolimus, mycophenolate mofetil (MMF), prednisone; [4]A/C/P (Regimen 1) – Azathioprine, cyclosporine, prednisone; C/M/P (regimen 3) – Cyclosporine, MMF, prednisone [5]DD – Deceased donor; [6]RLD – related living donor; [7]eGFR – estimated glomerular filtration rates. Ref. = referent.

3.4 eGFR MEASUREMENTS

Serial eGFR measurements over time are shown in Figure 3.18, below. In the group of patients without graft failure, eGFR trends were stable over time. Sparse and erratic data points in patients with graft failure gave rise to more extreme and uncertain eGFR trends. At each time point patients without graft failure had similar mean (SD) and median (IQR) eGFR values compared to those with graft failure (Figure 3.37).

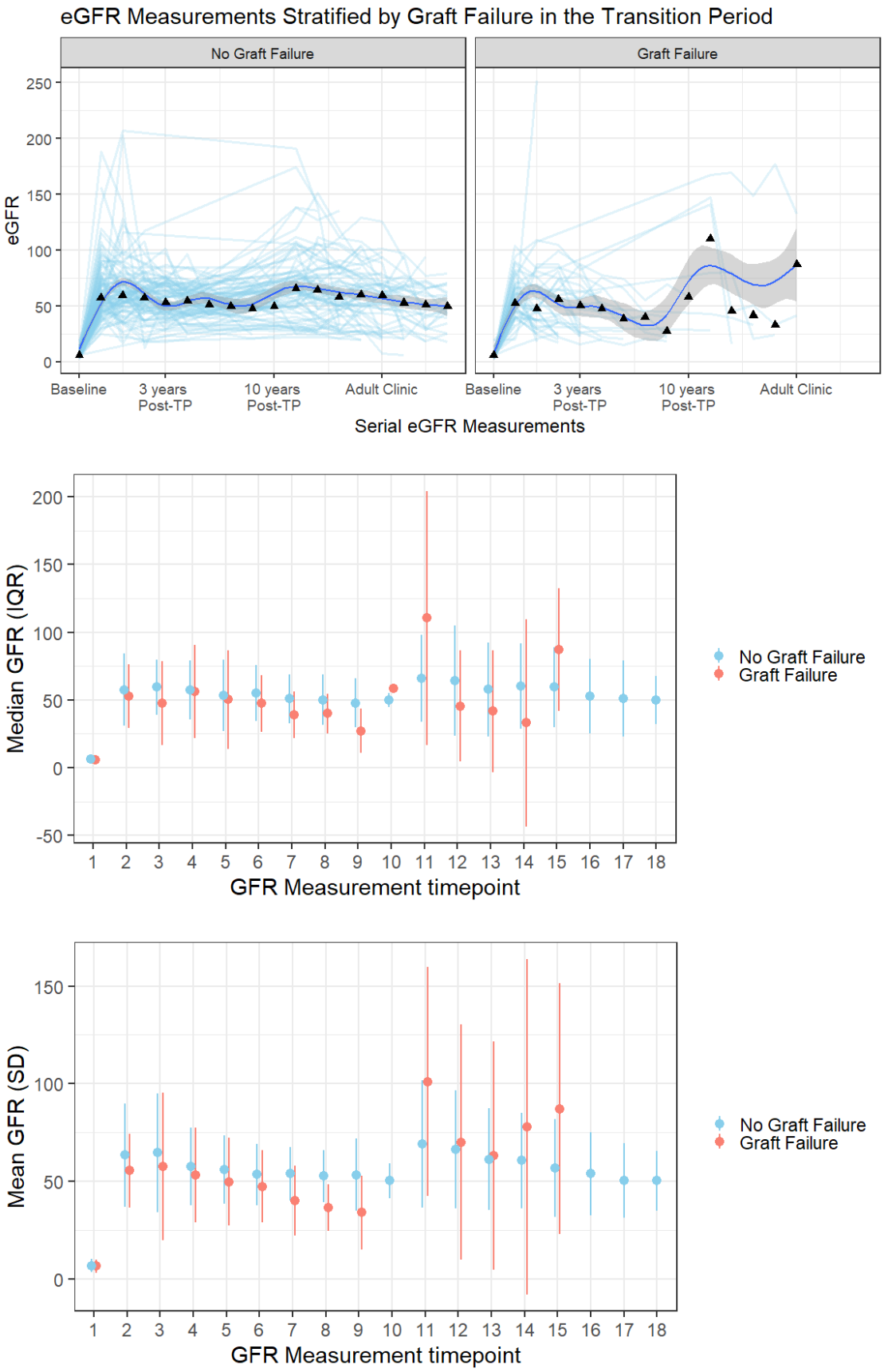


Figure 3.37: *Serial eGFR values with time*, stratified by graft failure

3.5 SECONDARY OBJECTIVES

3.5.1 HIV Infection

On analysis of the dataset, only 1 (0.6%) patient was found to have acquired an HIV infection. The patient acquired the infection through the graft, in which the father was the donor. The patient was subsequently started on anti-retroviral therapy (ART) during the study period. As the number was too small, this variable was not included in the survival analyses.

3.5.2 Pregnancy

No patients in our cohort fell pregnant.

4 DISCUSSION

There is a paucity of data in developing countries, and no data in South Africa, which looks at graft survival in adolescent renal transplant patients during the adolescent period and the transition from paediatric to adult care. This is the first such study done in South Africa. Studies in developed countries which have evaluated the transition of adolescent renal transplant patients have noted high rates of rejection, non-adherence, and allograft loss (46, 73). Transitions, in this context, are defined as periods between stages of a lifetime (67). In our study, adolescence was viewed as a transition period between that of childhood and adulthood, which are both considered to be stable states in human development (67). Furthermore, in our study, the transition period was defined as the planned movement of adolescents and young adults from the paediatric nephrology unit, to an adult-centred care system (74). This differed from transfer to an adult unit, in that transfer was the act of physically moving the adolescent patient from the paediatric unit, to the adult unit (74).

ESRD is uncommon in the paediatric population, the incidence and prevalence of which varies throughout the world (15). The USRDS showed an incidence of 13.7 per million population in 2015, compared to the UKRR, which reported an incidence of ESRD in children of 9.4 per marp in 2014 (25, 26). The highest reported incidence of ESRD in children was in New Zealand, with an annual rate of 18 per million children (15). Lower rates of 4 per million children were reported in Japan (15). As mentioned, there is paucity of data in the paediatric population in sub-Saharan Africa (27). A study done from South West Nigeria showed an incidence of ESRD of 4 per million children, compared to an incidence of 1-2 per million children in South Africa (27).

In patients with ESRD, the treatment of choice is renal transplantation (54). Renal transplantation has led to an improvement in the survival of children with ESRD, as well as improved quality of life (56).

However, there is limited availability of RRT in sub-Saharan African countries due to high costs and a lack of trained staff (75). Furthermore, renal transplantation is carried out in very few sub-Saharan African countries, South Africa being one of them (75). According to the Organ Donation Foundation in South Africa, 249 transplants were performed in 2016, of which only 4.8% (12 children), and 1.2% (3 adolescents) occurred in children and adolescents respectively (58). In comparison, in the USA, approximately 800 transplants are performed annually in children under the age of 18 years old (57).

The adolescent period is known to be a tumultuous period, and has been associated with a high rate of non-adherence to treatment (46). Adolescents have been shown to have the worst long-term graft survival amongst all paediatric age groups (7). Studies have shown that the adolescent period is one of vulnerability, with a high risk of rejection and graft failure (76). According to the NAPRTCS, this age group, along with the 6-12 year olds, had the highest number of rejections compared to other age groups (20). The UNOS database revealed that the adolescent group had the poorest 5-year graft survival, compared to other age groups (77).

However, with respect to outcomes following renal transplant, studies reported from the NAPRTCS registry, and the UNOS scientific registry (78, 79), showed that outcomes in the adolescent group, compared to those of adult renal transplant patients. A study done by El-Husseini et al (80), showed that 1-year and 5-year graft survival rates in the adolescent group, was 93.0% at 1-year and 75.0% at 5-year, compared to the adult group, at 92.0% and 72.0%, respectively.

The overall 1-year, and 5-year patient survival in the GRAFT-SAT study was 98.8%, and 95.1%, respectively, which compared favourably to international data (20). With respect to the graft survival for our study, at 1-year, the survival was 85.9%, however the 5-year graft survival was only 51.4%.

This was significantly lower compared to findings reported in the NAPRTCS registry, which showed 1-year and 5-year graft survival rates of 95.5% and 85.7% (1995-2010) in living donor renal transplantations, respectively (20). The 1-year and 5-year graft survival in our study, is significantly inferior when compared to international data. This difference could be attributed to the poor SES in our group, with resultant non-adherence and missed appointments. A study by Fabian et al (81), done at Donald Gordon Medical Centre, looked at paediatric primary kidney transplants, and showed a 10-year patient survival of >90%, and a 10-year graft survival of >85%. However, the authors noted that the study was small (n=51), with the possibility of imprecise estimates. Another South African study, which looked at paediatric renal transplant patients over a 20-year period, from 1984 to 2003, and which had similar numbers to our study, 10-year patient and graft survival rates were 68% and 23% respectively amongst 282 paediatric renal transplant patients (82). In comparison, our 10-year patient and graft survival rates were 93.9%, and 40.4%, respectively, which is significantly better (Table 4.1).

Table 4.1: Table comparing graft survival rates, internationally and locally

Graft survival	GRAFT-SAT Study (%)	NAPRTCS Registry[1] (20) (%)	Fabian et al (81) (%)	Pitcher et al (82) (%)
1-year	85.9	95.5	-	-
5-year	51.4	85.7	-	-
10-year	40.4	-	>85.0	23.0

[1]NAPRTCS Registry 2014 – North American Paediatric Renal Trials and Collaborative Studies (NAPRTCS) 2014 Annual Report.

The GRAFT-SAT study looked at renal transplants in the adolescent population at CMJAH over a 20-year period, from the 1st of January 1990 to the 31st of December 2010. During this study period, 255 grafts, for 188 patients occurred; however, 213 grafts, in 162 patients, met the inclusion criteria for this study, which were then used in the analysis. There were 61.0% males, compared to 39.0% females in this study population. According the NAPRTCS 2014 annual report, males comprised 59%

of their cohort (20), which was similar to our study group. In our study, however, sex was not found to contribute significantly to patient or graft survival.

With respect to race, the majority of the patients in our study were black, making up 49.4% and 53.5% of the patient and graft datasets, respectively. Race was not found to contribute significantly to patient survival, possibly as a result of the small number of deaths (n=7) with insufficient power to interrogate this variable adequately. However, with respect to graft survival, patients in the white group had significantly better graft survival, compared to patients in the non-white group (comprised of black, Asian, and mixed race patients). In our study, graft failure occurred during the adolescent period, in 64.0% black patients, in the paediatric and the adult units. There are numerous studies done in adult patients which show racial differences in kidney transplant outcomes, especially with respect to rejection and graft survival (61). However, there is a lack of paediatric data with regards the impact of race on graft survival. Several factors have been identified to contribute to reduced graft survival in black patients (61). These include, lower rates of RLD grafts, immunological factors, variability in absorption of immunosuppressive medications in black patients, higher rates of hypertension following renal transplantation, and the different causes of ESRD (61).

In our study, there was a similar distribution of the 'top 10' diagnoses for both the patient and graft datasets. The majority of the black patients, 48.3%, were classified among the group of diagnoses which included glomerular disease (APSGN, FSGS, FSH, GN, and RPGN). Glomerular disease is common in Africa, and is a significant cause of ESRD in sub-Saharan Africa (75). In addition, it has also been found to be of a more severe form, when compared to glomerular disease in Western countries, with resulting worse response to treatment (75). In the GRAFT-SAT study, patients who fell under the glomerular disease group had significantly poorer graft and patient survival using Kaplan-Meier estimates, compared to the group of patients with congenital diagnoses, or other

diagnoses. In univariate Cox proportional hazards regression modelling, glomerulonephritis was associated with significantly poorer graft survival than other diagnoses; however, in multivariate analysis type of diagnosis did not contribute significantly to patient, or graft survival.

In univariate survival analysis, SES played an important role in contributing significantly to patient and graft survival in our study, with patients of foreign, or unknown classification having worse survival rates compared to other groups. On multivariate Cox proportional hazards regression modelling (in which confounding factors were removed), patients of foreign or unknown SES had significantly poorer patient survival compared to patients of low, middle SES, or private classification. However, SES was found not to contribute significantly to graft survival. Studies have shown that in patients with financial constraints (with resultant missed appointments, lack of understanding of treatment adherence, and language barriers to name a few), this has led to an increase in non-adherence (46, 64).

Improvements in immunosuppressive regimens do not appear to have impacted on graft survival (83, 84). The goal of immunosuppressive therapy in renal transplant recipients is to balance the level of rejection rates, with the complications from side effects of the immunosuppressive regimens (85). In our study, the regimen containing tacrolimus, MMF, and prednisone (Regimen 2), was shown to significantly contribute to increased graft survival, compared to those patients on cyclosporine, MMF and prednisone (Regimen 3) or azathioprine, cyclosporine and prednisone (Regimen 1). However, multivariate Cox proportional hazards regression modelling showed that type of immunosuppressive regimen did not contribute significantly to graft survival. In general, tacrolimus is the preferred agent in the adolescent group, due to its relatively low side effect profile and increased immunosuppressive potency, compared to cyclosporine (85). Tacrolimus-based immunosuppression has also been associated with lower levels of acute rejection episodes (85). In addition, MMF compared to

azathioprine, has shown to be more effective in the prevention of acute rejection episodes, as well as having better long-term graft function (86). In the Paediatric Nephrology Department at CMJAH, there was a change in the main immunosuppressive regimen in the department from the year 2000. It was changed from the regimen including azathioprine, cyclosporine and prednisone (Regimen 1) to the regimen which encompassed tacrolimus, MMF and prednisone (Regimen 2).

The decade during which the patients in our study population were transplanted was found to impact on graft but not patient survival. Graft survival was significantly better in transplants conducted in the 2000's. From the 1980's, there have been significant improvements in short- and long-term graft and patient survival rates (87). An increase in both patient and graft survival in more recent years, may be attributed to improvements in pre-transplantation care, enhanced surgical techniques, better donor choices, more potent immunosuppressive medications, and use of evidence-based protocols (7). More effective immunosuppressive regimens, as of 2000, have been attributed by Guedes et al (87) as contributing to improved graft survival. In the GRAFT-SAT study, there was a move away from the use of cyclosporine and azathioprine, towards tacrolimus and MMF from 2000, which may have contributed to improved survival in recent years.

In our study, patients transplanted during the adolescent period, had significantly poorer graft survival, compared to patients <10 years old at transplant. However, adolescence was found not to significantly affect patient survival. Studies have shown that adolescent patients have the worst long-term graft survival amongst all paediatric age groups (7, 88). According to the NAPRTCS database, 5-year graft survival was poorest in the adolescent group (13-17 years old) (20). Patients in the adolescent group, were found to have the highest rate of non-compliance, with resultant high rate of graft failure (61). In our study, non-compliance was also found to significantly affect graft survival, as well as patient survival.

Recent studies have shown an improved half-life for DD and RLD renal transplants, at 13.8 years and 21.6 years respectively (83). A study by El-Husseini et al (80) showed that the relative risk of graft failure was higher in patients who received a graft from a DD, compared to those from an RLD. In our study, the majority of the patients (>60%) received a graft from a DD. In addition, 75.4% of the black patients in our study had received a graft from a DD (80). The type of graft impacted significantly on both patient and graft survival in our study, with patients who received an RLD graft having significantly better patient and graft survival compared to those who received a graft from a DD. Cox proportional hazards modelling failed to establish that type of graft was associated with better patient survival in our study, although RLD grafts were independently associated with better graft survival. In our study, the relationship of the donor to the recipient did not contribute significantly to graft survival. Studies have shown that there were no significant differences between graft survival of RLD grafts, compared to an unrelated living donor, though in most cases, the number of unrelated living donors were small (80, 89).

There are very few studies done showing the outcomes in paediatric renal transplant patients following subsequent renal transplantation (90). Studies done previously, have shown that survival of the first renal graft, is superior when compared to that of a second graft (90). A study done by Van Arendonk et al (90), showed that median graft survival was 11.6, 8.5, 7.7 and 4.5 years for the first, second, third, and fourth transplants respectively. In our study, median graft survival in patients who had one graft was 2120 days (5.8 years) (95% CL: 1813 to 3218 days), compared to 1021 days (2.8 years) (95% CL: 781 to 1682 days) in patients who received two or more grafts. Univariate analysis conducted in our study, revealed that patients who had two or more renal transplants had significantly worse graft survival, compared to the patients who received one graft in the study period. The total number of grafts received, did not significantly affect patient survival. Cox proportional

hazards regression model (multivariate analysis) showed that the total number of renal transplants did not affect graft survival.

This is the first South African study to look at graft survival in adolescent renal transplant patients during the transition period to the adult service. The transition of paediatric patients with chronic disease from childhood to adulthood, is accompanied by an increased need for patients to take on a more mature role, and to assume more responsibility for their condition and its treatment (46). There are concerns of non-adherence, with resultant allograft rejection or failure, in those patients not ready to assume responsibility for their condition (46). A study by Watson et al (59), showed a 35.0% allograft loss in the first 3 years post-transfer to the adult services if there was no transition clinic in place. In contrast, another study showed that the majority of adolescents transferred to adult services, were stable clinically 12 months following transfer (63). In that study, 11 patients were transferred to the adult service, 9 (81.8%) of whom remained clinically stable during the transfer, and 2 (18.2%) had worsening of their clinical status (63). In our study, transfer to the adult renal unit was associated with significantly better graft survival, compared to those patients who remained in the paediatric service. This was confirmed by the Cox proportion hazards regression model. Graft failure, during the adolescent period, occurred in 6 out of the 54 patients (11.1%) transferred to the adult nephrology unit, compared to 105 out of 162 (64.8%) patients who remained in the paediatric unit. One patient, who was transferred to the adult unit, had declining graft function prior to transfer, and subsequently lost the graft 79 days following transfer from the paediatric unit, due to non-compliance. The other five patients, however, had good graft function prior to transfer to the adult unit. Five out of the 6 patients who lost their grafts in the adult unit, did so because of non-compliance. The patient who lost the graft after 79 days, was the only 1 out of the 6 patients (16.7%), to have been non-compliant in both the paediatric and the adult nephrology units. Of the patients transferred to the adult unit, 48 (89.9%) had graft survival.

Seven (4.3%) patients demised during the adolescent period in our study, all of whom occurred in the paediatric unit. There were no deaths during the adolescent period in the adult unit, hence univariate analysis could not be conducted on patient survival in the adult unit.

With respect to the age at which the rejection episode occurred, the NAPRTCS database revealed that rejection episodes were significantly higher in the adolescent group compared to the infant group (p-value<0.001) (20). Studies have illustrated that rejection episodes occur largely as a result of inadequate immunosuppression in post-transplant patients, the adolescent group being the most at risk for this behaviour (91). Feinstein et al (91) showed that adolescents responsible for their own medication administration, had an overall incidence of non-adherence of 26.2%, compared to 3.0% in children <12 years, with a resultant increase in the number of rejection episodes. Multiple other studies also showed similar rates of non-adherence in the adolescent group, which far surpassed other paediatric age groups (59, 92, 93). In our study, 38.3% adolescent patients had rejection episodes in the study period, of whom 3.2% had rejection episodes prior to entering the adolescent period. Almost half (46.1%) of the adolescent patients in our study had more than one rejection episode. However, in survival analysis rejection episodes prior to or during the adolescent period did not affect patient or graft survival significantly.

The most important limitation in this study was the retrospective nature, which did not allow for accurate insight into clinical aspects of the study. Other limitations included small subject numbers in the study, missing patient data and records, and differences in record keeping between the paediatric and adult nephrology units.

5 CONCLUSION

Adolescent renal transplant patients are a vulnerable group, and have associated high rates of non-compliance, rejection, and graft loss (7). Studies have shown that the establishment of transitional clinics, and age-appropriate support groups, may have beneficial effects, including increasing adherence rates (91). Non-compliance is known to be multifactorial, and as such, should be managed by a multidisciplinary team in both the paediatric and the adult nephrology units, in order to improve communication between health care workers, their patients and families (91). Issues, such as suboptimal readiness to receive a transplant, and to transition into adult care when necessary, need to be addressed prior to the patient receiving a renal transplant, as this may lead to increased non-compliance (91).

In our study, multivariate analyses revealed that the parameters independently associated with worse graft survival included non-white race, adolescent age at the time of renal transplant, receipt of a DD graft, and retention in paediatric care.

From our study conducted, we would recommend a transition clinic be set up at CMJAH and other public sector hospitals that offer transplantation. Further research is needed to identify the precise factors involved in poor outcomes of adolescent renal transplant patients, especially in developing countries. These include the immunosuppressive regimen appropriate for our population, as well as looking at genetic factors, which may give a better understanding to the contribution to race.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Priya Darshani Chhiba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160405

NAME: (Principal Investigator)	Dr Priya Darshani Chhiba
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Graft Survival in South African Renal Transplant Patients during Patients the Transition Period at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Cecil Levy and Dr Claudia Do Vale
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/06/2016

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 in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the 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 review in April and will therefore be due in the month of April each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

27/06/2019

Dr PD Chhiba
School of Clinical Medicine
Department of Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital

Sent by e-mail to: chhiba.priya@gmail.com

Dear Dr Priya

Re: **Protocol Ref No: M160405**
Protocol Title: *Graft survival in South African renal transplant patients during the patients' transition period at Charlotte Maxeke Johannesburg Academic Hospital*
Principal Investigator: Dr PD Chhiba

Thank you for your letter of 06/06/2019.

I confirm that the proposed amendment has been noted and approved.

For the record, you intend to follow up on all patients in the Hospital now known as Charlotte Maxeke Johannesburg Academic Hospital, who, between 1990 and 2010, received a renal transplant and were, at the time of the transplant, aged between 10 and 19 years of age.

Thank you for keeping us informed.

Yours Sincerely

Mr I Burns
For the Human Research Ethics Committee (Medical)

Works2000/lain0007/Acknowledge.docx

APPENDIX B: TURNITIN REPORT

Submission date: 29-Nov-2019 03:50PM (UTC+0200)
Submission ID: 1223596035
File name: 0db69b3249_0_Turnitin_FINAL_DOCUMENT_CDV_DPM_PDC_28.11.2019.docx (378.48K)
Word count: 28449
Character count: 150813

0600356f:0_Turnitin_FINAL_DOCUMENT_CDV_DPM_PDC_28..

ORIGINALITY REPORT

1%	1%	2%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"American Transplant Congress 2007 Executive and Program Planning Committees and Abstract Review Committees", American Journal of Transplantation, 5/2007 Publication	1%
2	"Abstracts", American Journal of Transplantation, 5/2005 Publication	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		

APPENDIX C: PLAGIARISM DECLARATION CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I DR PRIYA DARSHANI CHHIBA (Student number: 0600356F) am a student registered for the degree of MASTERS OF MEDICINE, PAEDIATRICS in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 25/11/2019

APPENDIX D: RESEARCH PROTOCOL

GRAFT-SAT Study:

GRAFT survival in renal transplant South African patients in Transition

Graft survival in South African renal transplant patients during the transition period at Charlotte Maxeke Johannesburg Academic Hospital.

WITS Protocol Number: HREC: M160405

Revised Protocol:

10 March 2016

Investigators:

Dr Priya Darshani Chhiba

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Role on study: Primary Investigator

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Role on study: Supervisor

Dr Claudia Do Vale

Nephrology Fellow Department of Adult Nephrology, CMJAH

Tel: +27 11 933 9056

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Role on study: Supervisor

Summary:

The transition from childhood to adulthood can be a very confusing and vulnerable period in a child's life (1). It is made more complicated in children with chronic illness (1). Adolescents with chronic illnesses are compelled to transition from paediatric units to adult-centred care. Studies performed on the transition of adolescent renal transplant patients in the developed world have noted high rates of rejection, non-adherence and allograft loss (1,2). However, there is paucity of data in developing countries, and no data from South Africa addressing this issue. The purpose of this study is to assess the rates of acute and chronic rejection and ultimately graft survival in adolescents in a South African setting, at a Johannesburg Hospital as they transition into the adult care setting.

Background and justification:

The World Health Organisation (WHO) defines adolescence as “the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19 years, which represents one of the critical transitions in the life span” (3). Adolescence and young adulthood is well known to be a confusing and tumultuous time of life, regardless of physical health (2). With the transition into adulthood, adolescents and young adult patients move out of their comfortable, familiar paediatric environment into unknown and often much busier adult units, where they are expected to become more independent and take on increased responsibility for their own health (2,4).

There is a high risk of non-adherence in the adolescent age group for numerous reasons and they may be ill equipped to assume responsibility for their own health and medical condition (2). Previously accepted medical advice and guidance is now turned down and they have an increased tendency to reject authority (5). The physical changes which are associated with puberty, along with the natural tendency to explore and push boundaries, have a profound impact on the social and emotional functioning of adolescents in this time period (5). They tend to become more conscious of their body image, and dependency on their peers for approval and guidance is a common trait found amongst adolescents (5). Medical illness may impact greatly on many adolescents, making them feel different or imperfect in comparison to their peers (5).

An important component of adolescent development is that they are more impulsive and prone to participating in risky behaviours than their younger counterparts (5). There is a tendency to feel as though they are invincible and immune to their impulsivity (5,6).

Teenagers are unable to fully understand the long term outcomes of their lifestyle choices which includes experimentation with the use of alcohol and recreational substances, unprotected sexual activities and unsafe and thoughtless behaviours (5). The majority of adolescents with end stage renal disease have dealt with chronic illness from a very early period in their lives and they are unable to remember what it is to feel “normal” (7). Many children with chronic diseases may have had delayed onset of puberty and they may have witnessed other, healthy adolescents engaging in risky behaviours (7).

Entering adolescence and young adulthood puts these children with chronic diseases, at just as much risk of these unsafe behaviours as the general population, including engaging in sexual activity (7). Adolescents in the general population carry the highest burden of sexually transmitted infections (STI’s), and adolescent renal transplant patients are just as much at risk for these STI’s as healthy adolescents are (7). This was illustrated well in a study conducted by Ashoor and Pasternak, where it was found that there was a 30% STI prevalence in a review of adolescent renal transplant patients older than 13 years over a five year period (7).

Worldwide in 2012, there were about 2.1 million adolescents living with HIV (8). Statistics have also shown that of all new HIV infections, one seventh occur during the adolescent period (8). Adolescents in particular are vulnerable to HIV infection, especially when living in areas with HIV epidemic or if they are part of populations who are at increased risk for acquiring or transmitting HIV infection through sexual transmission as well as to dying from HIV associated causes (8). In South African adolescents, 37.5% had more than one sexual partner in the age group 15-24 year group compared to 18.3% in the 25 to 49 year old age group (9). In the age group 15 to 24 year old, the incidence of HIV is 7.1% and in the age

group 0 to 14 years the incidence is 2.4% in 2012 (9). According to the WHO, in low to middle income countries, annually, about 16 million girls aged 15 to 19 years and 1 million girls under 15 years old give birth (10). In 2014, the World Health Statistics showed a worldwide birth rate of 49 per 1000 girls aged 15 to 19 years old, they found that the highest rates were in sub-Saharan Africa (10).

It has been well documented that in patients with end stage renal disease (ESRD), the treatment of choice is renal transplantation (11). Renal transplantation has led to an improvement in the survival of children with ESRD, as well as an improved quality of life (12). However, the success of the renal transplant depends largely on compliance with immunosuppressive treatment (13). Studies have previously shown that adolescent and young adult transplant patients have the highest rates of acute and chronic rejection, following poor adherence, compared to the general transplant recipient population (14). There are numerous factors associated with increased non-adherence; these include low socioeconomic status, family instability, risk-taking behaviour and poor understanding of the importance of adherence to treatment, to name a few (12). The risk of non-adherence is further increased in adolescents or young adults who have not been sufficiently prepared for the transition into adult orientated health care systems (2). A study by Watson *et al* found a 35% allograft loss in patients in the first 3 years post-transfer of patients to adult care if a transition clinic was not in place (13).

A small number of studies in the developed world (high income countries) have shown the feasibility of establishing transition clinics and this has led to an increased graft survival in adolescent renal transplant patients (15). Transition clinics may serve as a stepping stone from paediatric to adult nephrology clinics whereby adolescents are assessed for their

readiness for transfer, as well as providing support and encouragement to the patient and to their families (12). Transition clinics can provide education to patients and to their families which would include information on immunosuppressive regimens, emphasis on adherence and consequences of non-adherence (12). Sexual behaviours, as well as recreational drug and alcohol use, are issues that would be addressed at these transition clinics (12). Unsafe sexual behaviour results in an increase in unplanned pregnancies, as well as new HIV infections, further complicating the management of these patients (7).

Prestidge *et al* performed a cohort study whereby they compared patient and allograft survival in renal transplant patients who received care from a transition clinic versus those who were transferred directly to the adult nephrology unit (14). The outcome showed that in the cohort directly transferred to the nephrology unit, 9% of patients demised and 21% had allograft rejection, which occurred within 12 months of transfer (14). This is compared to the group who received care from a transition clinic, in which no deaths or allograft losses occurred (14). The group managed by the transition clinic also maintained stable allograft function throughout the entire transition period and showed an improved and significant difference in two-year graft and patient survival (14).

Graft survival is the length of time where the transplant is functioning well enough to prevent the need for the recipient to either be initiated onto dialysis, to return onto dialysis or to require another renal transplant (16). Mclaren *et al* defined acute rejection by using clinical and biochemical data (17). This included an elevation of serum creatinine more than 15% above the baseline, a reduction in urine output and a response to antirejection therapy (17). They further stated that the majority of acute rejection episodes were confirmed by renal biopsy (17). The definition of allograft failure varies greatly in different studies. In one study

they defined chronic allograft failure as “progressive decline in renal function during the course of at least 3 months in the absence of another cause, for example, recurrent glomerulonephritis, renal artery stenosis or obstruction” (17).

On reviewing the available literature, only one article from India examined the outcomes of adolescent renal transplant patients during their transition period to adult care from developing countries (low to middle income countries) (18). Srivastava *et al* examined the adolescent outcomes of living donor transplant in the developing world compared to the developed world (high income countries) (18). They found early graft survival to be comparable to that found in the developed world, however the 5 year graft survival was markedly inferior at 66,8% compared to 85,7% in the developed world (18). The cause for this difference was suggested by the authors as being due to “*non-compliance with immunosuppressants necessitated by financial constraints”* (18). There is currently no literature available examining the outcomes of adolescent renal transplant patients within the South African setting.

Significant risk factors for graft survival include older recipient age, poor socio economic status, black race, diabetes, delayed graft function and the presence of rejection in the first year (16). Racial disparities in acute rejection and graft survival have been documented in both paediatric and adult renal transplant patients (19). Several factors may play a role in contributing to lower graft survival in black patients. These include; immunological factors, variability in absorption and effect of immunosuppressive medications in black patients, the different causes of ESRD and the incidence of hypertension (19). In our setting specifically language may also be a contributing factor to this inferior graft survival. English is the predominant language used in the Nephrology Clinic. For many of our patients, English is

not their first language and despite the use of language interpreters, misunderstanding of doctors' advice and recommendations regarding medication may also impact on outcome.

This study plans to assess the graft survival and health outcomes of adolescent renal transplant patients during their transition period from the paediatric to the adult nephrology department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Aim:

To assess graft survival and specific secondary health outcomes in children, at CMJAH during the transition period.

Objectives:

Primary:

1. To describe the graft survival in adolescents during the transition period.
2. To document the number of rejection episodes during the transitioning period.

Secondary:

1. To document the rate of decline in graft function during the transition period.
2. To determine patient survival up to five years post transfer.
3. To document the following secondary outcomes in our cohort:
    a. HIV infection
    b. Pregnancy

Study design:

Overview:

This study will be a retrospective analysis of adolescent patients who received a renal transplant between 1990 and 2010 in the Paediatric Nephrology Department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Permission to perform this retrospective study will be obtained from the Paediatric Nephrology and Adult Nephrology Departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), as well as the management of CMJAH. An application for ethics approval will be made to the University of the Witwatersrand Human Research Ethics Committee (Medical).

Study site:

The study will be conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Parktown. Data will also be collected from the Paediatric Nephrology Department as well as the Division of Adult Nephrology, Department of Internal Medicine at CMJAH.

Study population and period:

The patients included in this study will be those who have received a renal transplant between the years 1990 to 2010. These patients will have had a renal transplant in the Paediatric Nephrology Department and then entered the transition period whether or not they were transferred to the adult service.

Inclusion criteria include

- Patients were transplanted between 1990 and 2010
- They entered adolescence between 1990 to 2010
- They had a functioning graft at the time of adolescence

Exclusion criteria include

- Allograft loss prior to adolescence

We anticipate approximately 80 patients in our study sample. However, we cannot be certain as to how many of these patient files will be complete.

Study procedures:

Data collection:

The following variables will be collected:

Demographic characteristics

- Age (at transplant, on transfer to adults)
- Sex
- Race
- Hospital financial classification

Transplant

- Date of transplant
- Type of transplant (related live donor or deceased donor)
- The donor's relationship to the patient (parent, sibling or other)
- The number of transplants received
- Immunosuppressive regimens

Rejection episodes

Rejection episodes will be defined as an acute elevation of serum creatinine more than 15% above the baseline, a reduction in urine output and a response to antirejection therapy with or without renal biopsy confirmation (65).

- Date of rejection episodes
- Number of episodes
- Type of rejection episode
- Renal transplant biopsy results

Graft function

Graft failure will be defined as the need for the recipient to either be initiated onto dialysis, to return onto dialysis or to require another renal transplant (60).

- Serum creatinine levels and estimated glomerular filtration rate (eGFR) done at the time of transplant, two months following transplant, one year post transplant, before transition and at 21 years of age or death or graft failure will be recorded and analysed to determine changes in graft function.

Data entry and storage:

Each study subject will be allocated a random study identity number; this will ensure that all data capturing will be anonymously done. The patient's name and hospital number will be kept private and confidential at all times. Only the primary investigator will have access to the patient's details when allocating the random study identity number. Patient records will remain on hospital premises at all times as data capturing will be done on the site. Password protected software will be used for data capturing and storage under the random study identity number. No patient identifiers will be entered into the study database under any circumstances.

Data analysis:

Statistical analysis:

Descriptive results will be presented as means and standard deviations (SD), and medians and range will be used for continuous variables. Frequencies and percentages will be used for categorical variables.

Wilcoxon-Mann test (in paired measurements) will be used to compare creatinine levels between the time of renal transplant up to 5 years post transfer to the Adult Nephrology Department. Kaplan-Meier curve will be performed in order to calculate the median survival time after transfer.

Ethical considerations:

Risks:

This study poses minimal risk to the study subjects as it is a retrospective review. The main risk to the study subjects will be loss of confidentiality and all attempts will be made to ensure confidentiality is maintained. Information will be collected in a retrospective manner with no interaction of the primary investigator with study subjects. As mentioned above, a random study identity number will be issued to each study subject and all patient records will remain on hospital premises with data capturing done on site. No patient identifiers will at any time be entered into the database. These strategies aim to ensure that loss of confidentiality is minimised.

Benefits:

There will be no direct benefit to the study participants. The outcome of this study will hopefully assist in improving the transition period of adolescent renal transplant patients into adulthood in the future, within a South African setting.

Informed consent:

An application for ethics approval will be made to the University of the Witwatersrand Human Research Ethics Committee (Medical) for the conduction of this retrospective study. As this is a retrospective study, informed consent will not be required from the study participants as there are minimal risks to subjects.

Study costs:

This is a retrospective study and so no costs will be incurred to the participants. Study participants will also not receive payment in any form. All costs incurred by printing will be covered by the principal investigator.

Timeline:

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up - thesis												
Corrections												

Potential limitations:

The main limitations of this retrospective study will be an inability to obtain all the relevant data, damage to the patient's files or incomplete record keeping could also be a potential limitation of this study. Differences in the record keeping between the Paediatric and Adult Nephrology Departments could be a potential limitation of this study.

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