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PREDICTORS OF ONE-YEAR ALLOGRAFT FUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT KENYATTA NATIONAL HOSPITAL

BY

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STUDENT DECLARATION

I, Evans Arnold Onyango, do declare that this dissertation is my original work and has not been presented for a degree in any other institution of higher learning

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DEDICATION

I dedicate this work to my late maternal grandmother who believed in me unwaveringly, encouraged me persistently, and prayed for me fervently. Continue doing so.

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Finally, to God Almighty, where all the glory belongs. Thank You.

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LIST OF ABBREVIATIONS AND ACRONYMS

AKI—	**Acute Kidney Injury**
AOR—	**Adjusted Odds Ratio**
AR—	**Acute Rejection**
ARE—	**Acute Rejection Episode**
AZA—	**Azathioprine**
BMI—	**Body Mass Index**
CKTR—	**Chronic Kidney Transplant Rejection**
CIT—	**Cold Ischemic Time**
CKD—	**Chronic Kidney Disease**
CKD-T—	**Chronic Kidney Disease after Transplantation**
CNI—	**Calcineurin Inhibitor**
DCMT—	**Department of Clinical Medicine and Therapeutics**
DDKT—	**Deceased Donor Kidney Transplant**
DSA—	**Donor Specific Antibodies**
DTPA—	**Diethylenetriamine Pentaacetic acid**
DGF—	**Delayed Graft Function**
ERC—	**Ethics and Research Committee.**
eGFR—	**Estimated Glomerular Filtration Rate**
HLA—	**Human Leucocyte Antigen**
KFRT—	**Kidney Failure with Replacement Therapy**
KDIGO—	**Kidney Disease Improving Global Outcomes**
KDOQI—	**Kidney Disease Outcomes Quality Initiative**
KNH—	**Kenyatta National Hospital**
KRT—	**Kidney Replacement Therapy**
KTx—	**Kidney Transplantation**
LDKT—	**Living Donor Kidney Transplant**
LR—	**Logistic Regression**
MACE—	**Major Adverse Cardiovascular Events**
MDRD-4—	**Modification of Diet in Renal Disease (using 4 variables)**
MMF—	**Mycophenolate Mofetil**
NSAIDs—	**Non Steroidal Anti-Inflammatory Drugs**
OR—	**Odds Ratio**
PRA—	**Panel Reactive Antibodies**
SCr—	**Serum Creatinine**
VUR—	**Vesicoureteric Reflux**
WIT—	**Warm Ischemic Time**

DEFINITION OF TERMS

Acute allograft dysfunction is either an increase in serum creatinine of ≥25% from baseline or failure of the serum creatinine to decrease following transplantation or proteinuria >1 g/day. Acute allograft dysfunction can be immediate (<1week post-transplant), early (1 week to 3 months post-transplant) or late (>3 months post-transplant).

Chronic kidney transplant rejection or chronic rejection is defined as progressive decrease of renal graft function occurring more than 3 months post-transplant and manifesting one-year after the transplant and is usually accompanied by hypertension and proteinuria.

Chronic Kidney Disease is defined as abnormalities of kidney structure or function present for more than three months and classified based on cause of disease, level of glomerular filtration rate {GFR} (6 categories, that is G1-G5) and level of albuminuria (3 categories). CKD staging is based on estimated glomerular filtration rate (eGFR) and is categorized as follows; G1 is eGFR ≥ 90, G2 is eGFR of between 60-89, G3a is eGFR of between 45-59, G3b is eGFR of between 30-44, G4 is eGFR of between 15-29 and G5 is eGFR <15.

Kidney Failure with Replacement Therapy (previously End Stage Renal Disease) is defined as CKD G5 treated by dialysis or CKD G1-G5 after transplantation.

Allograft function describes how well the transplanted kidney is working using SCr based estimates of GFR.

Allograft survival is defined as the time between kidney transplantation and Kidney Failure with Replacement Therapy (KFRT).

Allograft failure is defined as return to dialysis or preemptive transplantation.

ABSTRACT

Background

The most favorable method of kidney replacement is kidney transplantation. Recipients undergo detailed pre-transplant preparation. However, there are cases of allograft failure preceded by poor allograft function. The aim of this study was to identify the predictors of allograft function in the transplant program and recommend measures to improve allograft survival.

Objective: To determine the association between predictors of allograft function, and allograft function at one-year among the Kenyatta National Hospital (KNH) transplant recipients.

Study methods: A retrospective cohort study among recipients of living donor kidney transplantation at KNH from 2010 to 2021. Predictor variables included demographic and clinical variables. The outcome variable was dichotomous; good allograft function (eGFR ≥60) or poor allograft function (eGFR <60). The eGFR at 1-year was computed using the MDRD-4 equation. Analysis utilized binary logistic regression.

Results: Data extraction was done from 177 recipient files. The recipient mean age was 37 years (S.D 13.2) and majority were males (74%). The donor mean age was 34 years (S.D 8.7) with more males (59%). The predominant pre-transplant comorbidities included hypertension (84%), glomerular diseases (36%), and diabetes mellitus (18%). The mean eGFR at one-year was 75.7 mL/min/1.73m2 (S.D 31.6) and majority were in CKD G2 (38.4%). The allograft survival rate at one year was 96%, while the patient survival rate was 94%. Predictors that were found to be associated with poor allograft function were; acute rejection O.R 9.2 (2.2-37.5), unplanned transplant related readmission O.R 8.8 (1.5-52.5), use of cyclosporine O.R 2.5 (1.3-4.2), serum creatinine at 6 months O.R 1.05 (1.01-1.08), and post-transplant day 1 urine output O.R 0.91 (0.67-0.93).

Conclusion: Acute rejection, unplanned transplant related readmissions, cyclosporine use and higher 6-month serum creatinine increased the risk of poor allograft function. While more urine output on post-transplant day 1 reduced the risk of poor allograft function.

CHAPTER ON
1.0 INTRODUCTION
1.1 Background

The two modes of kidney replacement therapy (KRT) are dialysis (hemodialysis and peritoneal dialysis) and kidney transplantation (KTx). Kidney transplantation is the preferred mode of KRT because it is associated with less morbidity and mortality.

Allograft function, determined by the estimated glomerular filtration rate (eGFR), predicts allograft survival and therefore the factors that affect allograft function also affect allograft survival. Despite this known fact, there are no studies in Africa investigating predictors of allograft function in resource limited settings. Most of the studies in transplant centers worldwide look at predictors of allograft survival or allograft failure.

Allograft survival rates are still declining in the kidney transplant program at KNH despite the detailed pre-transplant preparation and the use of living donors. Two studies done at KNH by Kayima et al (1) in 1996 and Githinji (2) in 2014 found the allograft survival rate at one-year post-transplant to be 93.3% and 92.01% respectively.

The allograft survival rate at one-year post-transplant in most transplant centers worldwide is more than 90%. The survival rate declines at five-years post-transplant to less than 90%. The following are examples of allograft survival rates at five-year post KTx; 85% according to the United States Renal Data System (USRDS) records, 89% according to Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, 85% in Pakistan, 60.7% in Nigeria and 80% in a study done in Cape Town, South Africa (3). At KNH, the allograft survival rate at four years post KTx was found to be 88.02% (2).

The decline in rates of allograft survival is due to factors that affect allograft function during the 1st year post KTx. These are predictors of allograft function and include the recipient and donor clinical characteristics, surgical techniques and competency of those involved in the multidisciplinary care and post-transplant variables including infection control, and the ability to identify and treat graft dysfunction among others (4).

Some of the predictors of allograft function may have an untoward result of poor graft function and subsequently lead to allograft failure. Allograft failure results in re-initiation of dialysis, re transplantation or death (5).

Previous studies have used different outcome variables of allograft survival and allograft failure and some only investigate individual factors such as the discharge creatinine value, post-transplant urine output, delayed graft function making it difficult to appreciate the effects of other confounding factors, while some investigate predictors in fewer combinations (5–8).

Studies on allograft function are lacking in Africa and therefore this study will bridge that gap and investigate the effect of several predictors on allograft function while controlling for other predictors. These predictors include; pretransplant predictors such as donor age, HLA match, and recipient sex and posttransplant predictors such as acute rejection, delayed graft function, opportunistic infections and unplanned transplant related reoperations and readmissions within the first year of transplant.

The results of this study will lead to precautionary strategies that will be aimed at improving kidney transplantation results and long-term allograft survival rates.

Improvements in allograft longevity is due to conservation of allograft function within the 1st year post-transplant (5) and therefore exploring these predictors of allograft function is important. Moreover, there is a shortage of transplant organs and therefore optimizing long term allograft survival is paramount.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Definition and Classification of CKD

Chronic Kidney Disease is defined as abnormalities of kidney structure or function present for more than three months. The CKD classification includes **C**ause of disease, level of **G**lomerular filtration rate {GFR} (6 categories) and level of **A**lbuminuria (3 categories). Kidney failure is defined as GFR <15mL/min/1.73m^2 or treatment by dialysis. Kidney failure with replacement therapy (previously End Stage Renal Disease) is CKD G5 treated by dialysis or CKD G1-G5 after transplantation (9).

Chronic Kidney Disease in the non-transplanted cohort and chronic kidney disease after transplantation (CKD-T) have a similar classification (Table 1).

Table 1: Current CKD nomenclature used by KDIGO

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories. Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				In mg/g <30 In mg/mol <3	30-300 3-30	>300 >30
GFR groups	G1	Normal or high	≥ 90			
	G2	Mildly reduced	60-89			
	G3a	Mildly-Moderately reduced	45-59			
	G3b	Moderately-severely reduced	30-44			
	G4	Severely reduced	15-29			
	G5	Kidney failure	<15			

Green: low risk of disease progression (if no other markers of kidney disease, no CKD), yellow: moderately increased risk, blue: high risk, red: very high risk

Adopted from Nomenclature for kidney function and disease (9)

2.2 CKD and CKD-T: Risk factors and prevalence

Post-transplant allograft function may not revert to the non-CKD kidney function. Once kidney function stabilizes post KTx, most recipients revert to CKD after transplantation stage 2 or 3 and can progress to allograft failure. Using data from the United Kingdom Renal Registry, Ansell et al (10) found the prevalence of CKD-T in 9542 post-transplant recipients to be; G1 (2.1%), G2 (21.6%), G3 (57.5%), G4 (15.7%) and G5 (3.1%).

The risk factors for CKD and CKD-T are similar and can be divided into; initiating factors that increase the risk of developing CKD and perpetuating factors that increase the risk of CKD progression to kidney failure with replacement therapy (KFRT).

In post KTx recipients, some of the initiating and perpetuating factors are established predictors of allograft function and operate mostly during the first-year post KTx resulting in allograft failure (11).

Examples of post-transplant predictors of allograft function include post-transplant diabetes mellitus (PTDM) previously referred to as new onset diabetes mellitus after transplant (NODAT), metabolic syndrome, low socioeconomic status, proteinuria, and smoking.

Table 2. CKD and CKD-T Initiating and perpetuating factors

Initiating Factors	Perpetuating Factors
Elderly	African-American race
Sex (male or female)	Protein in urine
Diabetes Mellitus	Obesity
Metabolic syndrome	Anemia
Primary kidney disease	Smoking
Urological disorders (urinary tract infections that recur, obstruction)	
Socioeconomic status	

2.3 Kidney Replacement Therapy

2.3.1 Dialysis

In Kenya, the most common mode of Kidney Replacement Therapy (KRT) is hemodialysis (1). According to The Canadian Society of Nephrology (12), patients with an eGFR less than 15 mL/min/1.73m^2 should be closely monitored by a nephrologist and chronic dialysis initiated when clinical indications emerge or the eGFR is 6 mL/min/1.73m^2 or less, whichever occurs first.

The standard of care for hemodialysis is 12 hours per week thrice-weekly. There are shorter treatment schedules in developing countries such as in Kenya due to a compromise of treatment efficacy, patient tolerance, acceptance and economic sustainability.

It is estimated that 4-10% of all dialysis patients were previously KTx recipients who developed allograft failure (13).

2.3.2 Kidney Transplantation

Kidney transplantation is the preferred mode of KRT because it is associated with less morbidity and mortality, better overall survival rates, better quality of life and lower economic costs (14,15). Life expectancy is projected to increase by 3-17 years in those who undergo KTx compared to those who receive chronic hemodialysis (16). Transplant recipients have the highest rate of allograft survival among all organs transplanted (17).

Kidney Disease Improving Global Outcomes (KDIGO) (18) recommends that all patients with CKD G4-G5 who are expected to reach KFRT be considered for kidney transplantation.

There are two types of transplantation i.e., living donor kidney transplant (LDKT) and deceased donor kidney transplant (DDKT). The LDKTs can be live related or live unrelated and have the benefit of better organ quality, shorter ischemia time and therefore better allograft survival rates (19). There is reliance on living related donors at KNH, no DDKT (20) but allograft survival rates are still declining in some KTx recipients.

The transplantation process varies from center to center with developed countries having better outcomes. The challenges in low resource settings include fewer nephrologists, limited resources, poverty and poor access to KRT (3). These challenges affect transplant preparation, post-transplant care, allograft function and thus allograft survival.

It is standard practice in developed countries to screen for donor specific antibodies (DSA) and therefore transplant only non-sensitized recipients resulting in less cases of acute rejection and allograft dysfunction (21). Social welfare including affordable healthcare is also available in developed countries, and this also has led to a positive impact on allograft survival compared to resource constrained settings.

2.3.2.1 The Kidney Transplantation Program at Kenyatta National Hospital

The first kidney transplant at KNH was performed in the year 1984. File records of these initial transplants are neither adequately documented nor readily available.

The current transplant program at KNH referred to the Interlife Kidney Transplant Program started in October 2009 and is run in partnership with Novartis Pharmaceuticals which helps with scientific and logistical support and capacity building.

Approximately 18 KTx are performed per year and since 2010 there have been a total of 210 KTx as shown in Figure 1.

The transplant program halted in 2020 when the Corona virus disease 2019 (Covid-19) was declared a pandemic but resumed the following year in 2021.

A study by Kayima et al (1) established that majority of donors and recipients at KNH were young male adults with mean ages of 36.7 and 32.6 respectively. The donors in most cases were siblings.

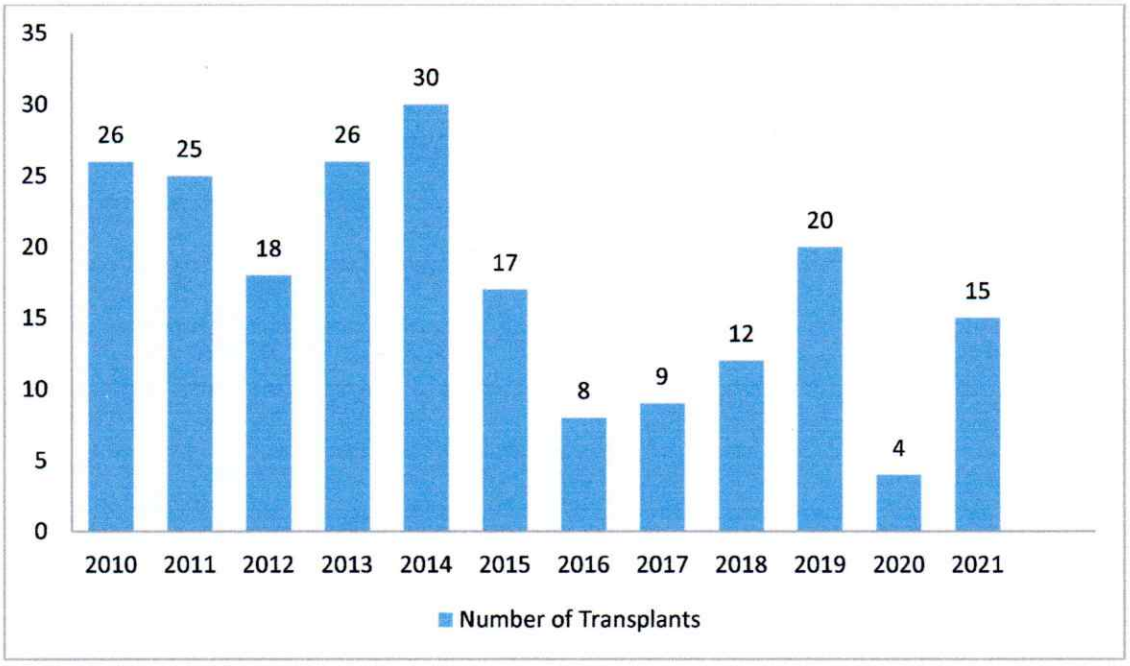
The KNH pre transplant evaluation of the recipient and donor is divided into 6 stages;

1. Stage 1: Counselling, informed consent, nutritional review and a thorough history taking from the donor and recipient.
2. Stage 2: Laboratory investigations including hematological, biochemical, immunological and microbiological tests.
3. Stage 3: Radiological investigations including chest radiograph, computed tomography angiography and echocardiogram.
4. Stage 4: HLA tissue typing (HLA A, B, DR and DQ) and T cell cross-matching.
5. Stage 5: Investigations to rule out other medical conditions for instance pap smear, prostatic specific antigen, and stool for occult blood. A pregnancy test for females.
6. Stage 6: A multidisciplinary team meets to review the results and a transplant date is set if the both donor and recipients are suitable for KTx

Transplants at KNH are performed via open nephrectomy as opposed to laparoscopic nephrectomy. The multidisciplinary team involved includes renal and theatre nurses, urologists, cardiothoracic surgeons, nephrologists, anesthesiologists and anesthetists, postgraduate residents in the respective departments, nutritionists among others.

The National Hospital Insurance Fund caters for the cost of transplant surgery; approximately Ksh 450,000 and Ksh 150,000 for the recipient and donor respectively. The recipient pays a deposit of Ksh 300,000 prior to the transplant to cater for the immunosuppressant therapy for the first-year post-transplant.

Figure 1: Number of Kidney transplants per year at KNH



2.4 Kidney allograft function

Preservation of function of a transplanted kidney is paramount, and to ensure this happens, monitoring is required. Monitoring of kidney function post-transplant utilizes serum creatinine (SCr) to calculate the estimated glomerular filtration rate (eGFR).

The higher the eGFR, the better the allograft function and higher SCr levels indicate poor allograft function. Allograft function at one year post KTx predicts long term allograft survival.

Elevation in SCr at 3- and 6-months post KTx is associated with lower allograft longevity and early allograft failure (16,22).

The predictors of allograft function also predict allograft survival and allograft failure. Additionally, strategies that improve allograft function will improve long term allograft survival (23).

2.5 Kidney allograft survival

Allograft survival is the time between kidney transplantation and Kidney Failure with Replacement Therapy (previously End Stage Kidney Failure).

Saidi (24) found the one-year allograft survival rate to be 77.8% in a study done between 1988 and 2001 at a private hospital in Kenya. The study identified acute rejection, readmission and female gender as factors that influenced allograft survival.

The one-year allograft survival rate at KNH in 1996 according to Kayima et al (1) was 93% and acute rejection was identified as the most common predictor associated with allograft survival. A more recent study by Githinji (2) in 2014 found the one-year allograft survival rate to be 92.01% and predictors that significantly influenced allograft survival included presence of systemic lupus erythematosus and lack of employment.

2.6 Kidney allograft failure

Allograft failure is defined as return to dialysis or preemptive transplantation. It usually occurs after many years in some kidney transplants.

Despite improvements in one-year allograft survival over the past decade, allograft failure rate after one year post KTx is between 3% and 6% per year (15). This allograft failure rate is linked to many recipient and donor factors that affect the outcome of the allograft. These factors are the established predictors of allograft function.

2.7 Established predictors of graft function

After a successful transplant, recipients regain good allograft function as the allograft stabilizes. A slow reduction in allograft function can occur after the stabilization.

The progressively declining allograft function may be due to many variables, including donor and recipient features, immunosuppression regimen, acute rejection and numerous other variables (25). These are predictors that are known to affect allograft function worldwide.

The predictors of allograft function vary from center to center majorly because of the resources available. Predictors that are operative in resource constrained transplant programs are different from the predictors in transplant programs in developed countries.

Table 3 shows the established predictors of allograft function.

Table 3. Established predictors of allograft function

Pre transplant donor factors	Pre transplant recipient factors	Factors during Transplantation	Post transplantation
Age	Age	Cold ischemic time	Urine output in the first 72hours after transplant
Sex	Sex	Warm ischemic time	Serum creatinine trend over 1-year post-transplant
BMI	BMI		Post-transplant diabetes mellitus
History of diabetes	History of diabetes		Immunosuppression regimen
History of hypertension	History of hypertension		Non adherence to treatment
Terminal SCr	Dialysis type		Acute rejection episodes
	Dialysis vintage time		Delayed graft function
	Immunological factors including prior sensitization (pregnancy or transfusion) and number of HLA mismatches		Socioeconomic variables including income, economic activity/employment status, public aid, marital status and family support
	Socioeconomic variables e.g level of education, employment status, marital status, insurance cover		Quality of life e.g, depression/exhaustion, impression of his/her health, level of satisfaction with therapy

2.7.1 Delayed graft function

Delayed graft function (DGF) is defined as the need for dialysis in the 1st week post-transplant. It is thought postulated that DGF occurs due to renal perfusion injury (26) resulting in high rates of allograft failure.

The DGF rate ranges from 5 to 40% in DDKT and 2 to 5% for LDKT.

Delayed graft function has increased in the Western countries partly due to the use of many marginal kidneys and scarcity of LDKT.

Prolonged cold ischemic time (CIT) and warm ischemia time (WIT), higher BMI (body mass index) and longer dialysis vintage time are strongly associated with DGF (27,28).

2.7.2 Cold and Warm Ischemia Time

Cold ischemia time (CIT) is defined as the interval between starting donor cold organ preservation at 4°C and removal of the allograft from cold storage. A CIT of less than 24 hours is acceptable. Prolonged CIT has a strong association with DGF and inferior long-term outcomes in deceased donor kidney transplantation (27).

Warm ischemia time (WIT) is the duration from interruption of circulation to the donor organ to the time it is flushed with normal saline (donor WIT) or the interval between removal of the allograft from cold storage and establishment of reperfusion in the recipient after unclamping of recipient vessels (recipient WIT).

The donor WIT is generally short and is of little consequence in open nephrectomies while the recipient WIT has a more significant effect on subsequent allograft function. The recipient WIT is also referred to as re-warming ischemia, anastomosis time or implantation time since it relates to this particular phase of the transplant procedure (29).

There is an association between prolonged recipient WIT and allograft failure and death and although there is consensus on keeping recipient WIT to a minimum duration, there is no consensus on the safe upper limit (30).

Marzouk *et al* (31) found that a WIT of less than 29 min was considered safe, while 2 European studies found that 30 and 34 min was safe (32) (33). A large Dutch study of LDKT (34) found that poor allograft function was present in 13% with WIT <30, 11% with WIT of 30–45 min, and the risk of allograft failure was increased 3-fold when WIT was >45 min. This Dutch study also shows that WIT < 30 min may not be entirely safe.

2.7.3 Acute rejection

Acute Rejection (AR) is defined based on either a histological diagnosis i.e., biopsy proven acute rejection (BPAR) that is subclinical rejection, or clinical acute rejection which is an episode of acute dysfunction of the allograft managed by at least 3 days of methylprednisolone pulse therapy.

Acute rejection in early post KTx results in loss of functional renal tissue that may represent the start of an insidious immunological process culminating in chronic rejection. Progressive decline in allograft function after treating AR may still occur affecting the residual functioning parenchyma (35).

The rate of AR has reduced from 50% to 15-20% within a decade with the introduction of modern immunosuppressive agents.

Delayed Graft Function is an independent risk factor for AR (4) and kidney allografts that experience DGF and AR are at a greater risk of poor allograft function.

2.7.4 Serum Creatinine

Estimated glomerular filtration rate (eGFR) is calculated using serum creatinine (SCr) and is used to assess progression of allograft function.

Creatinine is the parameter most frequently used post KTx (kidney transplant) to assess allograft function. Increased SCr means that there is a decline in viable kidney mass; as serum creatinine levels increase, allograft survival decreases (35).

Elevated SCr 1 year and 2 years post KTx is associated with a greater risk of allograft failure (35) and even much earlier serum creatinine elevation at 3- and 6-months post KTx is associated with allograft failure at 2 and 3 years.

Terminal SCr is the most recent donor serum creatinine value prior to transplant. Terminal SCr is a good measure of the donor kidney function; the lower the value, the lower the incidence of DGF (27).

Restricting factors for using SCr as a marker for eGFR include sex, age, body mass and race and the MDRD-4 equation for GFR estimation and other GFR estimation equations try to overcome some of these confounders (7).

The eGFR MDRD-4 (Modification of Diet in Renal Disease) is used in KTx recipients and is more precise compared to the Nankivell and Cockroft-Gault formulae for GFR estimation (36).

2.7.5 Infections

Cytomegalovirus (CMV) infection is the most common opportunistic infection after KTx.

The CMV-seronegative recipients who receive a kidney from a seropositive donor are at increased risk for CMV infection.

Cytomegalovirus infection is a risk factor for acute rejection and allograft failure.

The sero-prevalence of CMV in KNH transplant recipients has been shown to be very high (97.5%) but the majority do not progress to CMV disease (37).

The polyomavirus infection caused by BK virus is common in immunosuppressed KTx recipients. It begins viruria, then viremia, and if unchecked, results in nephropathy and allograft failure (38).

2.7.6 Proteinuria

Proteinuria is the daily protein excretion in urine more than the normal laboratory reference range. The detection of proteins in urine is used in assessment of kidney diseases and identifies the presence of kidney damage and the risk of worsening kidney function both before and after KTx (kidney transplant). Proteinuria in the setting of a normal eGFR is still a risk factor for progressive loss of allograft function.

The KDIGO transplant guidelines do not recommend the best method to quantify proteinuria and albuminuria post KTx but prefer the albumin-creatinine ration (ACR) and urine protein to creatinine ration (PCR) to urine dipstick (39). Urine dip stick is limited because it is less accurate in detecting and quantifying albuminuria (40).

In KNH, ACR and PCR are not routinely done post KTx. Dip stick urinalysis is test of choice and proteinuria is graded (in mg/dl) as negative (less than 10, trace (10 - 20), 1+ (30), 2+ (100), 3+ (300) or 4+ (1,000).

In patients with pre-transplant proteinuria, the amount decreases precipitously during the first three weeks post-transplantation (41).

Proteinuria is common after kidney transplant at low levels and it increases the risk of poor allograft function (42). The prevalence ranges from 7.5% to 45% according to the cutoff use.

Proteinuria at 12 months is one of the most crucial parameters related to allograft function decline.

2.7.7 Urine output

Urine output immediately post-transplant is considered a good marker of successful reperfusion (7). Urine output is the most easily acquired clinical parameter of allograft recovery and postoperative anuria or oliguria might suggest allograft injury (43).

The volume of urine is normally high during the first 24 to 48 hours post KTx. High urine volume in the first post KTx days result in good allograft function (44).

A study showed that KTx recipients with postoperative day one urine volume more than 10 liters had a good allograft survival while those with less than 2 liters were high risk candidates for poor allograft function (45). Another study found that postoperative day one urine volume could not be used to predict allograft function one year post KTx but day seven urine volume could be used (46). A retrospective study of 303 KTx recipients found that while post KTx urine output in isolation cannot predict 1-year allograft function, it can forecast the delayed graft function incidence (7).

Residual urine output is the recipient 24 hours urine output documented prior to transplant. This value has been correlated with post KTx urological complications that can result in allograft failure for instance urinary leaks and urethral stenosis. Absence of residual urine output for example is a risk factor of post KTx urinary leak (47).

2.7.8 Alloimmunization

Sensitization is a common cause of allograft failure through donor-specific antibodies (DSA) against HLA (human leucocyte antigen) (48). Allo-antibodies to HLA can result from transfusions, previous transplants or pregnancies.

Panel Reactive Antibody (PRA) test is used to assess sensitization to HLA prior to KTx. This is not done routinely in KNH. Higher PRA levels are related to a higher risk of allograft failure (49).

Nicol et al (35) found that patients who received blood transfusion were at higher risk of allograft failure 2 and 3 years after KTx.

Pregnancy has a stronger immunization effect than transfusion and as the more the pregnancies, the higher the HLA allo-immunization rate (49) (50). Alloimmunization due to pregnancy is a major cause of loss of living donor kidney transplantation because of the anticipated allograft dysfunction.

2.7.9 The immunosuppression therapy

Immunosuppression medication is divided into induction and maintenance.

Induction therapy plus maintenance immunosuppression is recommended rather that the latter alone. Induction therapy helps in lowering the incidence of early acute rejection especially in patients who are high risk for rejection including presence of preformed antibodies, multiple HLA mismatches, multiple comorbidities, being African American, high Panel Reactive Antibody levels and KTx with prolonged CIT (cold ischemic time).

Induction therapy includes basiliximab, alemtuzumab and antithymocyte globulin. Recipients with indications for induction therapy who don't receive the induction therapy are at greater risk of allograft failure.

Standard maintenance therapy in most modern immunosuppressive regimens includes a calcineurin inhibitor (CNI) (either cyclosporine or tacrolimus), an anti-metabolite (either azathioprine or mycophenolate mofetil) and prednisone.

Tacrolimus causes less acute rejection episodes, improved allograft function, and better allograft survival rates compared to cyclosporine or sirolimus which is an mTOR (mechanistic target of rapamycin) inhibitor. CIN nephrotoxicity contributes to the progression of CKD but this alone is not a common cause of allograft dysfunction.

Some studies on the efficacy of immunosuppression (51)(52) suggest that there is superior efficacy of MMF compared to AZA. The type and combination of maintenance immunosuppressant therapy used therefore influences post KTx allograft function.

2.7.10 Dialysis vintage

Dialysis vintage time is the total duration of any form of pre-transplant dialysis regardless of interruption. Allograft and patient survival are inversely related to dialysis vintage time.

Patients who receive a preemptive transplant (transplantation before initiating dialysis) or transplant after a short dialysis vintage time have greater allograft and patient survival rates compared to patients who received KTx (kidney transplant) after a longer dialysis vintage time (53).

Transplant recipients in the developed countries may have better rates of allograft survival because they are more likely to receive preemptive KTx and less likely to have more than 3 years of dialysis before KTx.

A small bladder resulting from long-term dialysis may increase the technical risk during surgery and the risk of vesicoureteric reflux (VUR) post KTx (47)(54)(55). The effect of VUR on allograft function is controversial as it did not reduce allograft function in some studies (56) (57) but together with pre transplant bladder capacity affected allograft function and survival in another study (54).

2.7.11 Socioeconomic variables

Socioeconomic variables have influenced health related outcomes since time immemorial.

Variables such as public welfare, income, healthcare availability, support from relatives are associated with successful transplantation (58). Those with lower socioeconomic status (SES) are less likely to have a successful KTx.

Lower SES comes with a higher risk of chronic illnesses, lower possibility of accessing healthcare and worse health outcomes in general. Higher education levels may improve health literacy, leading to a better compliance and a better allograft outcome.

Poorer patients are less likely to comply with post KTx immunosuppressive treatment and less likely to honor clinic visits. (58). This has a negative impact on allograft survival.

These socioeconomic parameters may not be commonly explored because most of them are not documented, are subjective or difficult to quantify.

According to the Kenya National Bureau of Statistics, majority of Kenyans are low-income earners (59).

2.7.12 Unplanned transplant related reoperation

Unplanned transplant related reoperation may be an important measure of the quality of a surgical procedure and is associated with increased hospitalization length, and hospital expenses (60). Unplanned reoperation usually has negative implications on allograft and patient outcomes (61).

2.7.13 Unplanned transplant related hospital readmission

Unplanned readmission refers to readmissions that are unpredictable after discharge from a KTx hospitalization.

There is no consistent definition of early hospital readmission (EHR) and late hospital readmission (LHR). Most studies use the following definition; EHR is ≥1 readmission within 30 days and LHR is any readmission between 31-365 days after discharge (62)(63).

There are numerous risk factors for readmission including; recipient gender, age, race and BMI, immunosuppression regimen, the length of stay for the transplant admission, comorbidities, and CMV infection (64).

Generally, most readmissions after organ transplantation occur in the first year (65) and readmissions are associated with an increase of over 50% in allograft loss and patient mortality (66,67). Unplanned readmissions also negatively affect the well-being of the recipient and the care takers, not to mention the financial burden and strain on the health care resources ((64,66))

McAdams-Demarco, et al (63,68) found that allograft survival was worse for KTx recipients who experience EHR. He also demonstrated that recipients who had EHR were likely to experience LHR as well.

Luan et al (69) demonstrated that unplanned hospital readmissions led to inferior clinical outcomes defined as patient and death-censored kidney survival.

2.7.14 Post-transplant Hypertension and Diabetes Mellitus

Hypertension in KTX recipients is associated with allograft dysfunction and subsequent shortened allograft and patient survival. Risk factors include CNIs (calcineurin inhibitors) and corticosteroids, transplant dysfunction in previously normotensive recipients.

Post transplantation diabetes mellitus formerly termed new onset diabetes mellitus after transplant (NODAT) also confers a worse allograft and patient survival.

2.8 Study justification

A successful kidney transplant program is based on a functioning allograft. This affords the recipient independence from hemodialysis and reduces the attendant morbidity and mortality.

There have been cases of allograft failure at Kenyatta National Hospital post-transplant despite sufficient pre transplant preparation and harvesting of kidneys from live healthy donors.

Allograft failure is a major pitfall to the kidney transplant recipient and the program and the community. It results in re-initiation of dialysis, re transplantation, economic and physical burden and even death.

There are no studies on predictors of allograft function in Africa and this study will bridge that knowledge gap identify the predictors that result in allograft failure in a resource limited setting such as KNH.

Identifying the predictors of allograft function will help inform strategies to improve renal transplantation results by improving allograft longevity, patient survival and quality of life. In a country with scarce resources and even fewer living donor kidney transplantations, safeguarding the available ones is crucial.

2.9 Research question

i. What are the factors associated with allograft function status in a transplant program in a resource limited setting?

2.10 Research Objective

2.10.1 Specific objective

i. To determine the association between known predictors of allograft function, and allograft function at one-year post-transplant among the KNH transplant recipients between 1st January 2010 and 31st December 2021.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

Retrospective Cohort Study

3.2 Study setting

This study was conducted at the Kenyatta National Hospital Renal Unit records department situated on the first floor of the old hospital building.

Kenyatta National Hospital is the largest referral hospital in East and Central Africa with a renal unit that is well equipped and well-staffed. The renal unit is situated on the first floor of the old hospital building. The transplant records are stored under lock and key, kept in good condition and can only be accessed after ethical approval. Transplant details of allograft recipients are well documented on a prescribed format that is available on all transplant records.

Approximately 150 patients undergo hemodialysis every week, peritoneal dialysis is also offered. The highest number of kidney transplants in Kenya are performed in KNH; that is approximately two transplantations are done every week.

3.3 Study population

Records of KTx recipients transplanted between 1st January 2010 and 31th December 2021.

The total number of transplants that took place during this period was 210.

The relevant donor details were as documented in the transplant protocol; therefore, no donor files were reviewed.

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion criteria

1. Medical records of all KTx recipients transplanted in KNH between 1st January 2010 and 31th December 2021 with one-year post-transplant follow up data.

3.4.2 Exclusion criteria

1. Kidney transplant perioperative mortalities (deaths occurring from entry into the operating theatre to 30 days after the transplant)
2. Kidney transplant mortalities occurring within 30 to 365 days after the transplant.

3.5 Sampling

In this study, Hseih Method (1998) for calculating sample size for logistic regression model was used (70).

The formula is shown below;

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{(P_1 - P_0)^2} \times \left[\left[\frac{P_0(1-P_0)}{1-\pi}\right] + \left[\frac{P_1(1-P_1)}{\pi}\right]\right]$$

Where;

n= The minimum sample size required to conduct meaningful statistical analysis.

α= Significance level; the likelihood of rejecting the H_0 when it is correct.

An alpha value of 0.05 was used.

P_0= The probability of having poor allograft function was taken as 0.6 meaning that the study assumed that 60% of the population at one level of any chosen covariate would have good allograft function.

P_1= The probability of having poor allograft function was taken as 0.4.

π=The portion of any covariate with poor allograft function.

In this study a value of 0.6 was used, meaning that the study assumed that 60% of the population at one level of any chosen predictor would have had good allograft function. This was derived from previous studies showing that around 60% had good allograft function at one-year post-transplant (10,71).

The sample size was calculated using a power of 90%.

The main assumption that was made in calculating the sample size was that the outcome variable was binomially distributed (the outcome variable only had two outcomes either good allograft or poor allograft function).

The values are shown below

$Z_{1-\alpha/2}$ =1.96

$Z_{1-\beta}$ = 0.84

P_1 = 0.4, P_0 = 0.6, π = 0.6 gives;

Putting the values in the formula, the computation gave; n = 156.8

Approximately **157** KTx recipients were sufficient to conduct a meaningful statistical analysis.

Considering the large number of predictor variables to be studied, the rule of thumb of ten events per variable (EPV) that is used in logistic regression analysis was applied to minimize overfitting (72). The population of kidney transplant recipients was 210 and this meant that 21 predictors (210/10) could be analyzed without overfitting.

Some predictors were eliminated from the study based their utility or how modifiable they were. In the variable selection, we used the clinical judgement of a consultant nephrologist and a clinical epidemiologist for elimination;

i. Predictors that are homogeneous in the population e.g., age of the recipient, BMI
ii. Predictors that are surrogates e.g., return to theatre, duration of dialysis
iii. Predictors that are non-specific e.g., employment status, marital status
iv. Predictors that were not accurately measured e.g., proteinuria.

3.6 Data collection

Data was extracted from file records and recorded on an online study proforma.

One Medical Officer who was trained and supervised by the principal investigator assisted in data extraction.

The principal investigator worked together with the Medical Officers and performed a re-entry on 10 percent of randomly selected files for comparison in order to maintain data accuracy and quality assurance.

3.7 Study variables

3.7.1 Outcome variable

Allograft function one year after KTx was the outcome or dependent variable.

The outcome variable was dichotomous, categorized as either good allograft function (eGFR $\geq$60) or poor allograft function (eGFR <60) using the estimated glomerular filtration rate (eGFR) as per KDIGO (Kidney Disease Improving Global Outcomes).

The eGFR was calculated using the MDRD-4 (Modification of Diet in Renal Disease) equation and Schwartz formula for recipients above and below 18 years respectively. The 12-month post-transplant serum creatinine was used to perform this eGFR calculation.

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3.7.2 Predictor Variables

The predictor variables or independent variables were both continuous and categorical in nature.

3.7.2.1 Pretransplant variables

Donor specific variables

1. Age as completed number of years at date of transplant.

Recipient characteristics

1. Sex
2. Education; this is the highest level of education attained was recorded as primary level, secondary level. tertiary level or no formal education.
3. Residual urine output; this is the recipient 24-hour urine output produced prior to transplantation and was recorded as yes if any amount of urine was produced.
4. History of pregnancy; this is prior sensitization through pregnancy and was recorded as yes if there was a history of ever being pregnant.
5. HLA match; this ranges from 0 to 6 is the number of HLA matches between a donor and a recipient from the HLA cross match results. It was categorized as 0-2 and 3-6. The more matches between the donor and the recipient the better.

3.7.2.2 Post transplantation variables

1. The calcineurin inhibitor utilized; this is a choice between tacrolimus and cyclosporine that was initiated during the transplant admission.
2. The antiproliferative agent utilized; this is a choice between mycophenolate mofetil and azathioprine that was initiated during the transplant admission.
3. Acute rejection episode; this is defined as a histological diagnosis or documented therapy for acute allograft dysfunction with methylprednisolone for at least three days within one year post KTx.
4. Delayed graft function; this is defined as the requirement for dialysis within the first week of transplant.
5. Post-transplant 24-hour urine output; this is the amount of urine produced in 24 hours. It was calculated and recorded in ml/kg/hr for standardization and to compensate for the difference in demographic data such as weight.

i. Post-transplant Day 1
ii. Post-transplant Day 2
iii. Post-transplant Day 3

6. Unplanned transplant related hospital readmission; this is any readmission related to the allograft occurring within one year post KTx that is not planned after discharge from a transplant hospitalization.
7. Unplanned transplant related reoperation; this is any secondary procedure performed within one year post KTx due to a complication resulting directly or indirectly from the transplant operation.
8. Urinary Tract Infection; this is any urinary tract infection within one-year post-transplant diagnosed using urinalysis or urine culture and sensitivity and treated with antibiotics.
9. Acute kidney injury; this is defined as an increase in serum creatinine to 1.5 times baseline or more or urine output less than 0.5mls/kg/h for 6 hours documented during the transplant admission.
10. Post-transplant mellitus (PTDM); this is a documented diagnosis and use of glucose lowering agent within one-year post-transplant.
11. Opportunistic infections; these are opportunistic infections within the first-year post KTx (e.g., cytomegalovirus disease, polyoma BK virus, tuberculosis, toxoplasmosis, pneumocystis, cryptococcus, herpes virus infections and candidiasis) recorded as yes or no.
12. Serum creatinine post KTx in μmol/L
    i. SCr at 3 months
    ii. SCr at 6 months

3.8 Data Analysis

3.8.1 Descriptive Statistics

All categorical variables were presented as percentages and proportions. The continuous variables that were normally distributed were presented as means with standard deviations.

3.8.2 Binary Logistic Regression Model

In this study, logistic regression was used to determine the association between predictors of allograft function among kidney transplant recipients and allograft function.

In the univariate binary logistic regression, a p-value ($P < 0.05$) was used as a cutoff for significance. All the variables from in the univariate stage were used to fit a multivariate binary logistic regression model.

The multivariate binary logistic regression model used several predictor variables while controlling for all the variables. A p-value ($P < 0.05$) was used as the threshold to determine significant predictors of allograft function at 1 year post transplant.

Odds ratio with a 95% confidence interval was then computed to describe the magnitude and direction of the association.

The presence of outliers was tested using a scatterplot and out of range data points and outliers, were dropped before any analysis was carried out.

Multicollinearity was tested using Variance Inflation Factors.

SAS was used to analyze data for this study.

3.9 Ethical considerations

Approval and permission was sought from the DCMT and the KNH/UON ERC.

Authority to use the medical records at KNH was sought from the Head of Department renal unit before data collection.

There was no contact with patients as this was a review of records.

Patient records were anonymized and there was no unique patient identifier in the data set that could be used to trace back to the patient.

All data collected is kept in an online server that I can access and all the electronic data is password protected.

The study proforma materials will be stored by the principal investigator for a period of 5 years or upon registration as a specialist, whichever occurs earlier.

The findings, conclusions and the recommendations of the study will be forwarded to the head of department of the renal unit, KNH after presentation of the results to the department of clinical medicine and therapeutics.

CHAPTER FOUR
4.0 RESULTS

A total of 210 kidney transplants were performed at Kenyatta National Hospital (KNH) between 1st January 2010 and 31st December 2021. We excluded the following during screening;

Twelve (12) missing recipient files, one (1) recipient file with no records and eight (8) recipient files with less than one year followed up data because they were transplanted after 30th June 2021. Nine (9) recipient files that had perioperative mortalities; 1 died intraoperatively, two died on the 2nd post-transplant day, one died on the 3rd post-transplant day, one died 15 days post-transplant, 2 died 1-month post-transplant and 2 died 3 months post-transplant. One (1) recipient file indicating transplantation in another center.

Therefore, a total of 179 files belonged to recipients transplanted between 1st January 2010 and 30th June 2021.

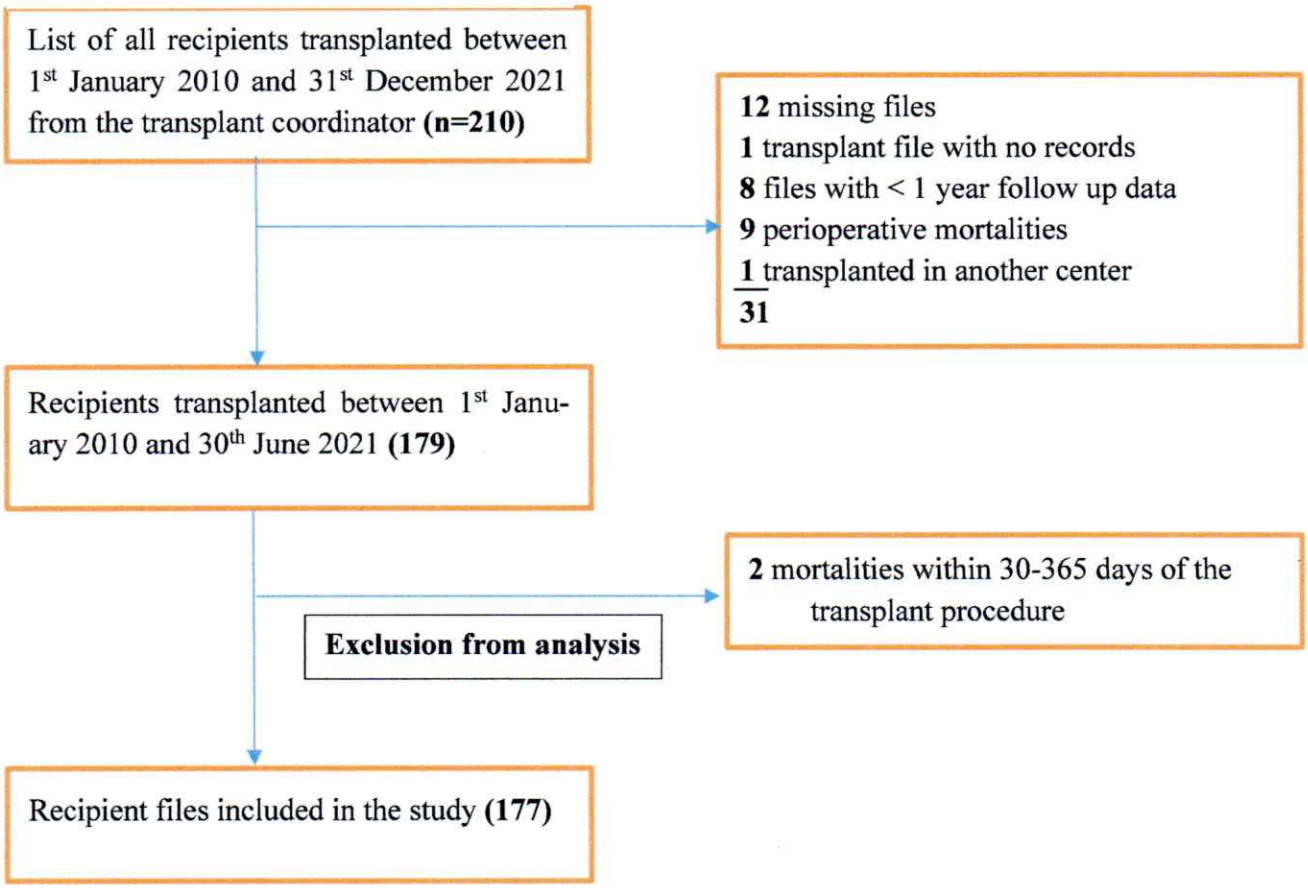
Two (2) recipients were excluded from the analysis because they did not have the outcome of interest recorded. Of the 2, one died 4 months post-transplant and one died 5 months post-transplant.

A total of 177 recipient files met the study inclusion criteria and were therefore included in the study.

One year patient survival

There were 190 recipient files that were available in the renal unit and 2 were excluded from this calculation (KTx in India and missing records). Out of the 188 recipients, 11 died within the first year of transplant and therefore the one-year post-transplant survival rate was 94% (177/188).

Figure 2: Records selection flow diagram



4.1 Descriptive statistics of pre-transplant predictors of allograft function

4.1.1 Recipient and donor socio-demographic characteristics

Among the 177 KTx recipients, majority were males 74% (131/177) while 26% (46/177) were females. A total of 53.7% attained a tertiary level of education. The transplant recipient age range was from 10 years to 66 years with a mean age of 37 years (S.D 13.15). The recipient mean BMI was 21.8 (S.D 4.42).

Majority of donors were males at 59% (105/177). The donor age range was from 21 years to 57 years with a mean donor age of 34.4 years (S.D 8.72). Table 4 shows characteristics of the recipients.

Table 4: Recipient and donor socio-demographic characteristics

Recipient socio-demographic characteristics	
Variable	**Frequency (%)**
Sex	
Male	*131 (74%)*
Female	*46 (26%)*
Education	
No formal education	*1(0.6%)*
Primary level	*27(15.3%)*
Secondary level	*54(30.5%)*
Tertiary level	*95(53.7%)*
Age (S.D)	
Mean	*37 (S.D 13.2)*
Median	*35*
Min	*10*
Max	*66*
BMI (S.D)	
Mean	*21.8 (S.D 4.4)*
Median	*21.5*
Min	*17.5*
Max	*33*

Donor socio-demographic characteristics	
Sex	
Female	*72(41%)*
Male	*105(59%)*
Age (S.D)	
Mean	*34 (S.D 8.7)*
Median	*33*
Min	*21*
Max	*57*

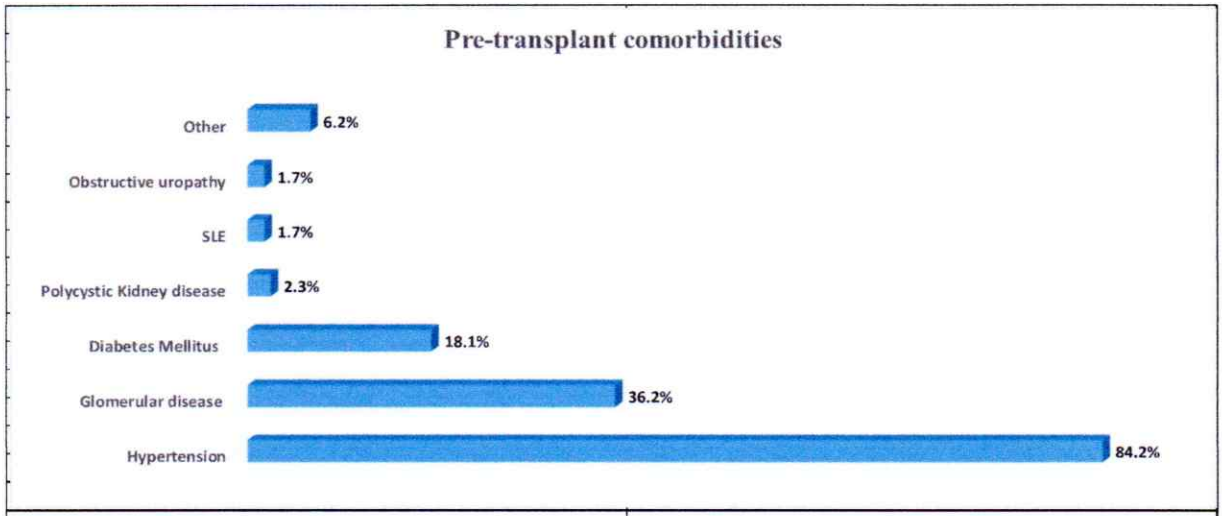
n=177, S. D=standard deviation, Min=Minimum, Max=Maximum

4.1.2 Recipient clinical characteristics

Comorbidities

The most common pre-transplant comorbidity was hypertension at 84% followed by glomerular disease at 36% and diabetes mellitus at 18%. Among the recipients with glomerular diseases, 16 out of 64 had a documented biopsy diagnosis. Obstructive uropathy, polycystic kidney disease and systemic lupus erythematosus accounted for 1.7%, 1.7% and 2.3% respectively. Other comorbidities included Alport's syndrome, renal oncocytoma, primary hyperoxaluria, NSAID-induced nephropathy, gouty arthritis and rheumatoid arthritis. There were 87 recipients who had more than one comorbidity. Figure 3 shows the pretransplant comorbidities.

Figure 3: Pre-transplant comorbidities



Hypertension	149 (84.2%)
Glomerular disease	64 (36.2%)
Diabetes Mellitus	32 (18.1%)
Polycystic Kidney disease	4 (2.3%)
SLE	3 (1.7%)
Obstructive uropathy	3 (1.7%)
Other	11 (6.2%)

SLE=systemic lupus erythematosus

History of sensitization through pregnancy

Sensitization through pregnancy was evident in 63% (29/46) of the female recipients while 37% (17/46) did not have history of sensitization through pregnancy.

HLA Match

The most common HLA match category was 3 to 6 at 67.2 % (119/177) while 32.8% (58/177) had a HLA match of 0-2.

Pre-transplant residual urine output

A majority of the recipients (86.4%) had pretransplant residual urine output while 13.6% (24/177) did not have residual urine output.

4.2 Post-transplant predictors

All recipients were put on one calcineurin inhibitor (CNI) and one antiproliferative agent as maintenance immunosuppressants. The CNIs used were tacrolimus at 51.4% (91/177) and cyclosporine at 48.6% (86/177). The antiproliferative agents used were mycophenolate mofetil at 95.5% (169/177) and azathioprine at 4.5% (8/177). All the recipient were on prednisone.

Acute rejection occurred in 32.8% (58/177) of KTx recipients during the first year of transplant, delayed graft function occurred in 5.7% (10/177) during the first year of transplant and acute kidney injury during the transplant admission occurred in 8.5% (15/177).

Urinary Tract Infections (UTIs) occurred in 19.7 % during the first year of transplant.

Post-transplant diabetes mellitus (PTDM) occurred in 11% (20/177).

Table 5: Recipient post-transplant clinical characteristics

Variable	Frequency (%)
Calcineurin inhibitor used as immunosuppressant	
Tacrolimus	91(51.4%)
Cyclosporine	86(48.6%)
Antiproliferative agent used as immunosuppressant	
Mycophenolate mofetil	169(95.5)
Azathioprine	8(4.5%)
Acute Rejection	
Yes	58(32.8%)
No	119(67.2%)
Delayed Graft Function	
Yes	10 (5.6%)
No	167 (94.4%)
Acute Kidney Injury during the transplant admission	
Yes	15(8.5%)
No	162(91.5%)
Urinary Tract Infection within the first year of transplant	
Had UTI	35(19.7%)
No UTI	142(80.3%)
Post-transplant diabetes mellitus	
Yes	20(11.3%)
No	157(88.7%)

Unplanned transplant related hospital readmissions

During the first year of transplant, 62.7% (111/177) had at least one unplanned transplant related readmission; 30 were readmitted twice, 24 were readmitted thrice and 12 were readmitted more that thrice.

Table 6: Frequency of unplanned post-transplant hospital readmissions

Frequency of readmission	**Number readmitted**
1	**45**
2	**30**
3	**24**
4	**10**
5	**1**
6	**0**
7	**1**

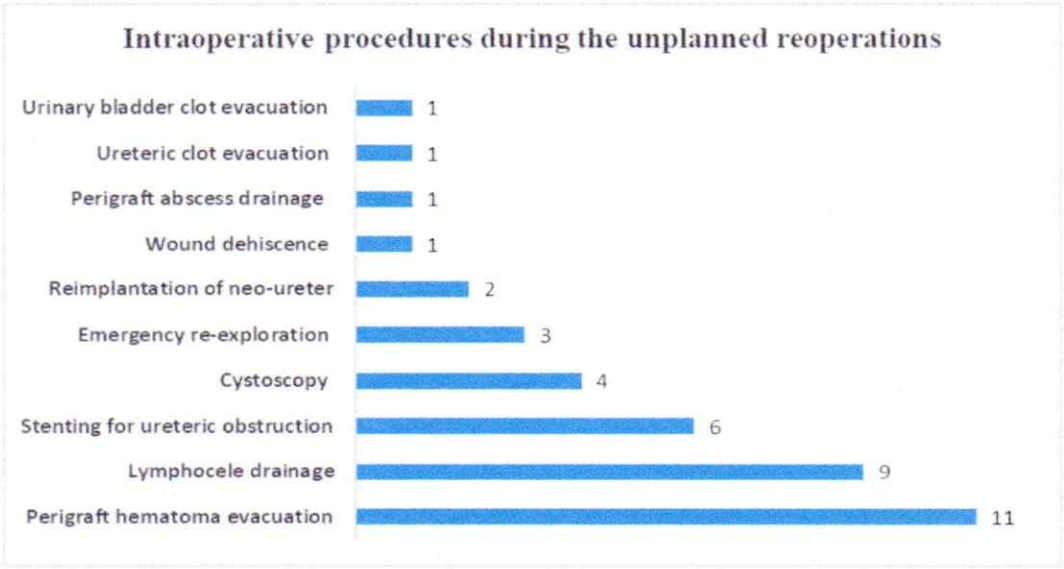
n=111

The readmission rate within the first year of transplant was 62.7%.

Unplanned transplant related reoperations

Unplanned transplant related reoperations occurred in 15.8% (28/177). The most common secondary procedures performed during the reoperation were perigraft hematoma evacuation, lymphocele drainage and stenting for ureteric obstruction as shown in Figure 4. Some recipients had more than one procedure performed

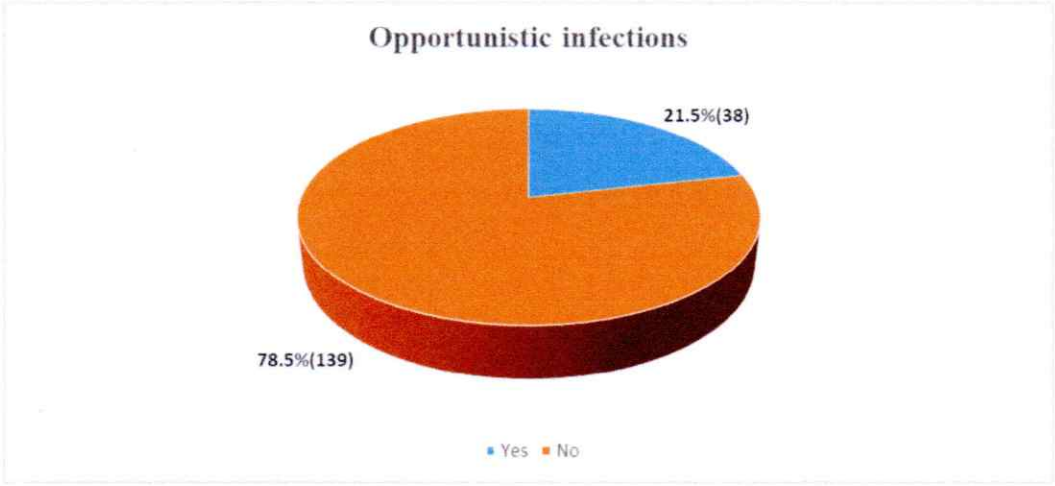
Figure 4: Intraoperative procedures during the unplanned reoperations



Opportunistic infections within 1 year

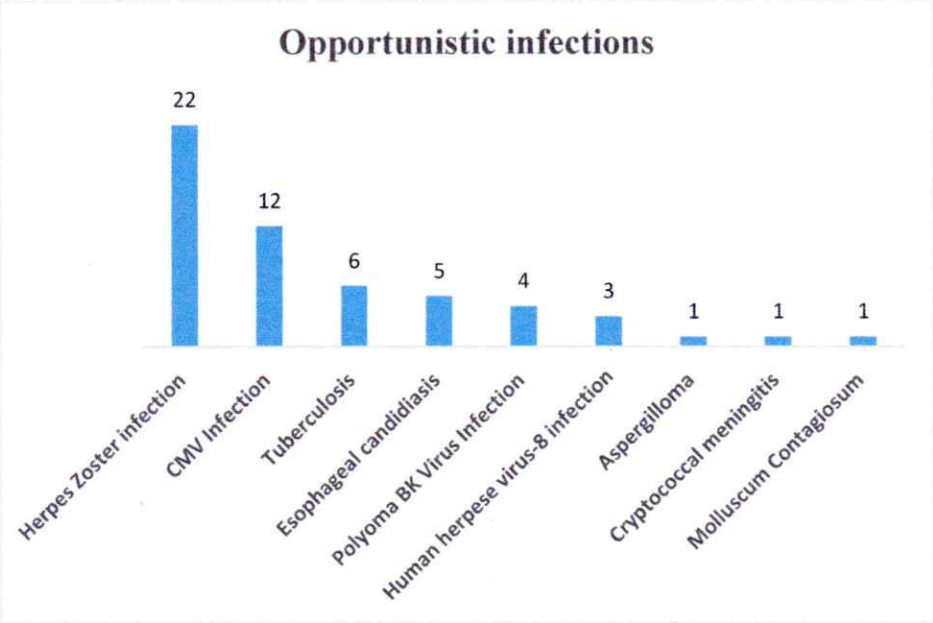
Opportunistic infections occurred in 21.47% (38/177). The most common opportunistic infection was caused by herpes virus and included Herpes Zoster Infection, Cytomegalovirus Infection and Human Herpes Virus-8 as shown in Figure 6. There were recipients who had more than one opportunistic infection.

Figure 5: Opportunistic infections within 1 year



n=177

Figure 6: Type of opportunistic infections within one year of transplant



CMV-cytomegalovirus

Post-transplant urine output

The 24-hour urine output on the first three days post-transplant was and recorded in mls/kg/hr. The mean post-transplant day 1 urine output was 8.9 mls/kg/hr (S.D 3.6), the mean post-transplant day 2 urine output was 5.5 mls/kg/hr (S.D 2.6) and the mean post-transplant day 3 urine output was 4 mls/kg/hr (S.D 1.76).

Table 7: Post-transplant urine output in the first 3 days of transplant

Post-transplant D1 urine output	
Mean	8.9 (S.D 3.6)
Median	8.6
Min	0
Max	23.9
Post-transplant D2 urine output	
Mean	5.5 (S.D 2.6)
Median	5.5
Min	0
Max	13.5
Post-transplant D3 urine output	
Mean	4.0 (S.D 1.8)
Median	3.8
Min	0.1
Max	9.3

n=177, S. D=standard deviation, Min=Minimum, Max=Maximum

Serum creatinine

The mean serum creatinine (SCr) at discharge, 3 months, 6 months and 12 months were 142.9 µmol/L (S.D 96.8), 136.3 µmol/L (S.D 90.2), 127.2 µmol/L (S.D 43.3) and 125.9 µmol/L (S.D 60.4) respectively.

Table 8: Serum creatinine at different time periods

	SCr at Dis-charge	**SCr at *3 months***	**SCr at *6 months***	**SCr at *12 months***
Mean	142.9 (S.D 96.8)	136.3 (S.D 90.2)	127.2 (S.D 43.3)	125.9 (S.D 60.4)
Median	113	117	123	114
Min	45	49.7	125	44
Max	622	449	346	562

n=177, S. D=standard deviation, Min=Minimum, Max=Maximum, SCr=Serum Creatinine

4.3 Estimated glomerular filtration rate at one year

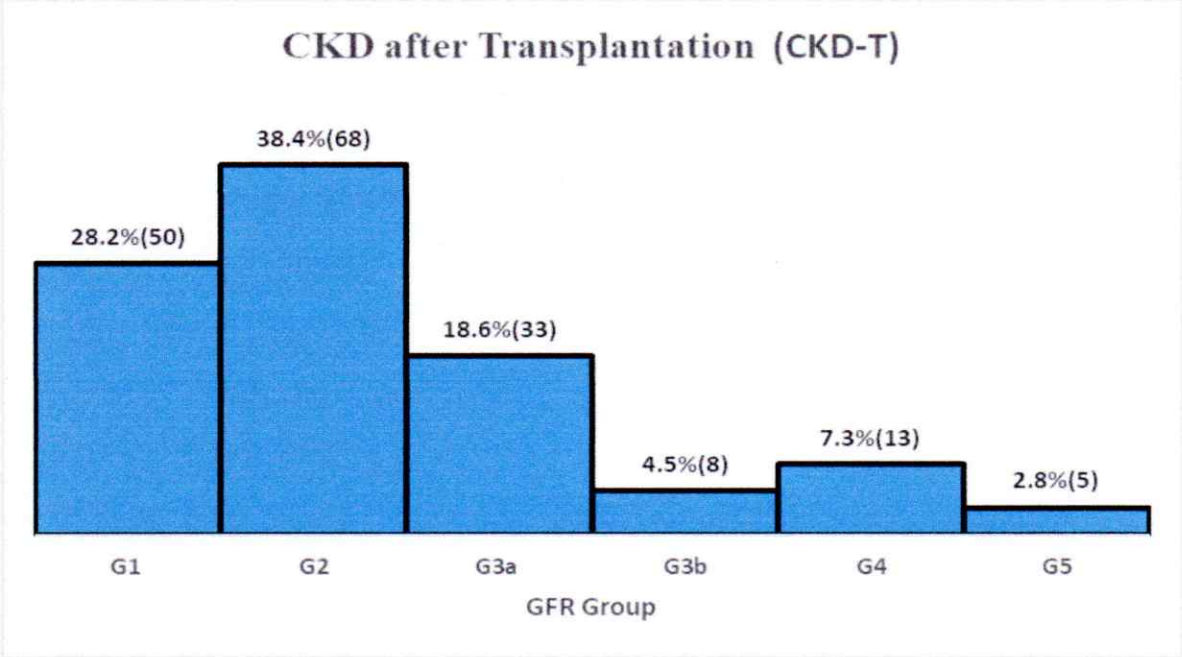
The mean eGFR at one-year post-transplant was 75.7 mL/min/1.73m^2 (S.D 31.6). The lowest eGFR was 10.2 mL/min/1.73m^2 and the highest was 169.4 mL/min/1.73m^2. Majority of recipients were in CKD G2 at 38.4% (68/177) as shown in Figure 7.

Table 9: Estimated glomerular filtration rate at 1-year

Estimated glomerular filtration rate	
Mean	75.7 (S.D 31.6)
Median	76.1
Min	10.2
Max	169.4

n=177, S. D=standard deviation, Min=Minimum, Max=Maximum

Figure 7: Chronic Kidney Disease Staging by KDIGO at 1 year



n=177, S. D=standard deviation, Min=Minimum, Max=Maximum

One year allograft survival

A total of 7 recipients had allograft loss and returned to dialysis within the first year of transplantation. This gives a one-year allograft survival rate of 96% (170/177).

4.6 Fitting the Binary Logistic Regression Model

Our test for multicollinearity using variance inflation factor values found none of the predictor variables to be correlated with each other hence the data was suitable for fitting the model.

Unadjusted and adjusted odds ratios were computed for the 21 predictors that were analyzed. This was done by computing the odds ratio one predictor at a time in the univariate stage and adjusting for all the other predictors in the multivariate stage respectively.

Predictors of poor allograft function

Variables associated with increased risk of poor allograft function at one-year in the univariate stage were; use of cyclosporine compared to tacrolimus with 1.2-fold odds (1.09-2.30), azathioprine vs mycophenolate mofetil with 6.8 fold odds (1.32-34.57), acute rejection with 5.6 fold odds (2.82-11.16), delayed graft function with 5.3 fold odds (1.32-21.35), unplanned transplant related reoperation with 2.4 fold odds (1.05-5.42), UTI post-transplant with 2.3 fold odds (1.09-4.95), opportunistic infections with 3.5 fold odds (1.62-7.15), and unplanned transplant related readmissions with 14.7 fold odds (4.98-43.12) as shown in Table 10.

The post-transplant day 1 and day 2 urine output was associated with 18% (OR 0.82) reduced odds and 26% (OR 0.74) reduced odds of poor allograft function respectively for every unit increase in urine output in ml/kg/hr. The association of the total 24-hour urine output in post-transplant day 2 (26% reduced risk) and day 3 (22% reduced risk) with allograft function was quantitatively similar, however did not reach statistical significance. The SCr at 3 months and 6 months was associated with 4% (OR 1.04) and 5% (OR 1.05) increased odds of poor allograft function respectively for every unit increase in SCr in μmol/L. The SCr OR at 3 months was quantitatively similar to SCr at 6 months, however did not reach statistical significance in the multivariate stage. This is demonstrated in Table 11.

Out of all the predictors that were significant in the univariate stage, only five were independent predictors in the multivariate stage. The predictors that were associated with poor allograft function were; acute rejection with 9.2-fold odds (2.23-37.51), unplanned transplant related readmissions with 8.9-fold odds (1.49-52.50), choice of CNI use (cyclosporine vs tacrolimus) with 2.5-

fold odds (1.28-4.18) and serum creatinine at 6 months post-transplant; with every unit increase of serum creatinine in μmol/L being associated with a 5% (1.02-1.08) increased risk.

The only variable associated with reduced risk of poor allograft function as an independent predictor was the post-transplant day 1 urine output; with every unit increase in urine output in mls/kg/h being associated with a 9% (OR 0.91) reduced odds of poor allograft function.

The following predictors were not significantly associated with an increased odds of poor allograft function in the univariate analysis; a lower number of HLA match of 0-2 with 1.4 odds (0.71-2.72), primary level of education with 1.6 odds (0.57-4.29), acute kidney injury during the transplant admission with 2.2 odds (0.79-6.25) and post-transplant diabetes mellitus with 1.4 odds (0.55-3.71)

The following predictors were not independently associated with a reduced risk of poor allograft function at the univariate analysis; female sex with 0.65 odds (0.31-1.38), absence of pretransplant residual urine output with 0.82 odds (0.32-2.11), secondary level of education with 0.84 odds (0.42-1.68), sensitization through pregnancy with 0.75 odds (0.22-2.58), and donor age with 0.99 odds (0.96-1.03) as shown in Table 10.

Table 10: Odds Ratio Table for Predictors of Allograft function (Categorical Variables)

	Predictors	Allograft Function		Odds Ratio	
		Poor (n=58) 32.7%	Good (n=119) 67.3%	Unadjusted (95% CI)	Adjusted (95% CI)
1	**Recipient sex**				
	Female	12(26.68%)	34(28.57%)	0.65 (0.31-1.38)	0.587 (0.04- 9.12)
	Male (ref)	46(79.31%)	85(71.43%)		
2	**Number of HLA matches**				
	(0-2)	22(37.9%)	36(30.3%)	1.41(0.71-2.72)	0.43 (0.12-1.54)
	(3-6) (ref)	36(62.1%)	83(69.7%)		
3	**Pre transplant residual urine output**				
	No Residual output	7(12.1%)	17(14.3%)	0.82(0.32-2.11)	0.41(0.16-4.52)
	Residual output(ref)	51(87.9%)	102(85.7%)		
4	**Education**				
	No formal education	0(0%)	(0%)	NC	
	Primary level	7(12.1%)	21(16.8%)	1.56(0.57-4.29)	0.61(0.08-4.69)
	Secondary level	19(32.8%)	35(29.4%)	0.84(0.42-1.68)	0.442 (0.10-1.94)
	Tertiary level (ref)	32(55.2%)	63(52.9%)		
5	**History of sensitization: Pregnancy**				
	Yes	10(58.2%)	19(65.5%)	0.75(0.22-2.58)	0.14 (0.01-2.77)
	No(ref)	7(41.8)	10(34.5%)		
6	**Choice of calcineurin inhibitor**				
	Cyclosporine	30(51.7%)	56(47.1%)	1.23(1.09-2.30)	2.48(1.28-4.18)
	Tacrolimus (ref)	28(48.3%)	63(52.9%)		
7	**Choice of antiproliferative agent**				
	Azathioprine	6(10.3%)	2(1.7%)	6.75 (1.32-34.57)	4.90(0.02-20.55)
	Mycophenolate mofetil (ref)	52(89.7%)	117(98.3%)		
8	**Acute Rejection**				
	Yes	34(58.6%)	24(20.2%)	5.61(2.82-11.16)	9.16(2.23-37.51)
	No(ref)	24(41.4%)	95(79.8%)		

		Allograft Function		Odds Ratio	
	Predictors	**Poor (n=58) 32.7%**	**Good (n=119) 67.3%**	**Unadjusted (95% CI)**	**Adjusted (95% CI)**
9	**Delayed graft function**				
	Yes	*7(12.1%)*	*3(2.5%)*	*5.31(1.32-21.35)*	*1.03(0.07- 14.22)*
	No(ref)	*51(87.9%)*	*116(97.5%)*		
10	**Unplanned transplant related reoperation**				
	Yes	*14(24.1%)*	*14(11.8%)*	*2.39(1.05-5.42)*	*2.48(0.49-12.52)*
	No(ref)	*44(75.9%)*	*105(88.2%)*		
11	**Acute kidney injury during the transplant admission**				
	Yes	*8(13.3%)*	*7(5.9%)*	*2.22(0.79-6.25)*	*0.48(0.05-4.58)*
	No(ref)	*50(86.2%)*	*112(94.1%)*		
12	**UTI Post-transplant**				
	Had UTI	*17(29.3%)*	*18(15.1%)*	*2.33(1.09-4.95)*	*0.55(0.13-2.34)*
	No UTI (ref)	*41(70.7%)*	*101(84.9%)*		
13	**Post-transplant diabetes mellitus**				
	Yes	*8(13.9%)*	*12(10.1%)*	*1.43(0.55-3.71)*	*1.21(0.90-5.92)*
	No(ref)	*50(86.1%)*	*107(89.9%)*		
14	**Opportunistic infections post-transplant**				
	Yes	*21(36.2%)*	*17(14.3%)*	*3.45(1.62-7.15)*	*1.54(0.32-7.42)*
	No(ref)	*37(63.8%)*	*102(85.7%)*		
15	**Unplanned transplant related readmission**				
	Yes	*54(93.1%)*	*57(47.9%)*	*14.68(4.98-43.12)*	*8.85(1.49-52.50)*
	No (ref)	*4(6.9%)*	*62(52.1%)*		

CI=confidence interval, NC=not computed

Table 11: Odds Ratio Table for Predictors of Allograft Function (continuous variables)

	Predictor	*Unadjusted OR (CI)*	*Adjusted OR (CI)*
16	***Post-transplant day 1 urine output***	*0.82 (0.73-0.91)*	*0.91(0.67-0.93)*
17	***Post-transplant day 2 urine output***	*0.74(0.61-0.91)*	*0.87(0.54-1.40)*
18	***Post-transplant day 3 urine output***	*0.78(0.56-1.03)*	*0.94(0.52-1.69)*
19	***Serum creatinine at 3 months***	*1.04 (1.01-1.05)*	*1.01 (1.00-1.02)*
20	***Serum creatinine at 6 months***	*1.05(1.03-1.06)*	*1.05(1.02-1.08)*
21	***Donor age***	*0.99(0.96-1.03)*	*1.05(0.97-1.13)*

CI=confidence interval

CHAPTER FIVE

5.0 DISCUSSION

5.1 Discussion

This study set out to determine the predictors of one year allograft function in the transplant program in a resource limited setting.

In the univariate analysis, the following predictors operate in our setting; the choice of calcineurin inhibitor (CNI) and antiproliferative agent, acute rejection, delayed graft function, unplanned transplant related reoperation, urinary tract infections (UTIs), opportunistic infections (OIs) and unplanned transplant related readmissions within the first year of transplant.

The post-transplant day 1 and day 2 urine output and the serum creatinine (SCr) at 3 months and 6 months were also predictors.

In the multivariate analysis, only five predictors were independent predictors of poor allograft function. These predictors were; acute rejection (AR), unplanned transplant related readmission, cyclosporine as the CNI, post-transplant day 1 urine output and SCr at 6 months.

Other studies have also found these predictors to be significant in their population in both univariate and multivariate analysis (3,5,22,23,73–79).

Most of the studies that investigate predictors that affect the allograft use allograft failure or allograft survival as the outcome variable. They therefore use a different statistical test of association such as cox proportional hazard ratio. Because the direction and magnitude of association of the predictors to the outcome variable is the most important comparison, and the predictors of allograft function also predict allograft survival and allograft failure, we were able to compared our study to these studies.

A study done at the Kenyatta National Hospital and Aga Khan University Hospital by Atuhe et al found AKI within the first year to be significantly associated with allograft function AOR 13.2 (1.96-88.05) (80).

Saidi et al (24) in Kenya found AR (p=0.016) to be associated with allograft survival although Fischer's exact test was used to test for association in this study.

A study by Kayima et al (1) in 1996 found acute rejection to be associated with allograft survival at Kenyatta National Hospital (KNH). However, this was a small study of 15 transplant recipients, seven of whom developed AR.

Although not statistically significant, Davidson et al (3) in Tunisia found AR to have a moderately increased risk of allograft failure on multivariate analysis. This study used cox proportional analysis, HR 1.58 (0.59-4.23).

There are predictors that were not significantly associated with allograft function in the univariate analysis and multivariate analysis yet they are established predictors in other centers in the developed countries like the United States of America, New Zealand and Australia. These included; recipient sex, number of HLA matches, pre transplant residual urine output, level of education, history of sensitization through pregnancy, acute kidney injury during the transplant admission, post-transplant diabetes mellitus and donor age.

These might have been non-significant because our outcome variable was allograft function. In transplant research, the same covariates are commonly used with different outcome parameters including allograft function, allograft survival and allograft failure and this determines the study design (81).

Our population was a black African population which included patients with a mean age of 37 years compared to studies in developed centers that include elderly recipients (age above 65 years) and have a higher mean age of recipients (23,82–87). These transplant centers also perform both living donor and deceased donor kidney transplantation (35,77) unlike our facility that only performs LDKT which has superior outcomes compared to DDKT.

Transplant centers elsewhere include recipients with comorbidities that did not feature prominently in our population such as chronic lung diseases, heart failure, cerebrovascular accidents, connective tissue diseases and Human Immunodeficiency Virus.

There were predictors that could not be measured accurately and were therefore missed or misdiagnosed, for example; being a retrospective study, we could not verify whether the diagnosis of acute kidney injury was based on the KDIGO definition or erroneously on any elevation of serum creatinine. Opportunistic infections might also have been missed due to limitation of performing diagnostic tests such as CMV polymerase chain reaction (PCR) and viral load, and kidney biopsies. Urinary tract infections might have been missed because only urine dipstick tests were done and not urine cultures. Additionally, infections might have been diagnosed and treated in other facilities and therefore not captured.

It is also possible that the predictors were not found to be significant due to a chance error.

In our study there was a 9-fold increased risk of recipients who had acute rejection (AR) within one-year developing poor allograft function.

A study by Pinaki et al found a 2.9-fold increased odds of allograft failure in recipients with acute rejection on multivariate logistic regression (88). A study of 63,045 KTx recipients found Acute rejection to confer a significant relative risk of between 1.67 to 5.2-fold for allograft failure at different time points (89).

Atuhe et al in Kenya found AR to have 2.57-fold increased odds (0.77-8.51) of poor allograft function. Although this was not statistically significant but the upper limit of the CI almost approached our odds of 9.2 (80).

The higher risk of poor allograft function in our recipients with AR might be because we mostly use the clinical diagnosis of AR which tends to overestimate the number of AR episodes. Comparatively, AR diagnosis in advanced transplant centers is biopsy proven (90).

Acute rejection is an independent predictor of poor allograft function and therefore the cause should be investigated and interventions made. Pre transplant Donor Specific Antibodies (DSA) and Panel Reactive Antibodies (PRA) are common causes of acute rejection and poor allograft function that we did not investigate (91,92). Screening for these antibodies is not routinely done in our setting and should be incorporated in the pre transplant screening stage. Patients on cyclosporin who develop AR should be switched to tacrolimus because it is known to reduce episodes of AR (15,93).

Recipients who had unplanned readmissions were 8.8 times more likely to have poor graft function at 1 year.

Most studies categorize unplanned hospital readmissions into early hospital readmission (EHR) and late hospital readmission (LHR) (63,66,69). We did not categorize readmissions as EHR (within 30 days) and LHR (between 31 and 365 days).

McAdams-Demarco, et al (63,68) using the United States Renal Data System found the EHR to be associated with an increased risk of allograft failure HR, 1.43 (1.36–1.51). Nguyen et al found 3.8-fold odds of allograft failure (1.44-10.00) in recipients who had EHR (62).

This is an independent predictor that needs to be mitigated, however we did not study the indications for readmission and therefore a prospective study to identify the causes of readmissions and interventions to improve outcomes is necessary.

Cyclosporine use compared to tacrolimus was associated with a 2.5-fold increased risk of developing poor allograft function at one-year post-transplant.

This is similar to studies that showed that tacrolimus was superior and more potent that cyclosporine (15,93). A study by Knoll et al (94) on predictors of allograft survival that compared tacrolimus vs cyclosporine found a reduced odds of allograft failure 0.95 (0.65-1.40).

A Cochrane review of 123 reports from 30 studies found recipient on tacrolimus to have a relative risk reduction of allograft failure of 0.56, CI 0.36-0.86) (95).

The better performance of tacrolimus is because it is very potent and results in lower rates of acute rejection. Additional factors include a reduction in maintenance steroid dose and a decreased need for antihypertensive drugs (15,93,94).

Tacrolimus should therefore be the calcineurin inhibitor of choice for our transplant recipients.

There was a 10% reduced risk of having poor graft function at one-year post-transplant for every unit increase of urine output in the first day of transplant.

Urine output in the first seven days post-transplant is associated with allograft function (7,44,46)

A retrospective study of 158 recipients showed that more than 10 liters of urine produced on day 1 post KTx was associated with good short- and long-term allograft function (45).

A systematic review of nine studies found the posttransplant day 1 urine output to be significantly associated with allograft function (96). One of the studies found a 15.7-fold increased risk of poor allograft function with reduced urine output, CI 8.78 - 28.00.

Lai et al found the urine output on the post-transplant day 7 to be significantly associated with allograft failure in the multivariate analysis but not post-transplant day; p-values were used, no odds ratios or CIs were provided (46).

Although the appropriate urine volume after KTx has not been documented in literature, a large volume of urine output points to successful allograft perfusion and absence of obstruction.

This positive association in our study is because a large volume of urine output immediately after transplant is an indication of good allograft uptake.

Proper monitoring of urine output in the post-transplant day 1 is therefore vital and interventions should be made when there is reduced urine output e.g., allograft ultrasound to detect vascular thrombosis and ureteric obstruction which are common causes of reduced urine output (97).

This study demonstrated that there was a 5% increased risk of developing poor allograft function for each unit increase in SCr at 6 months.

Prommool et al found a higher SCr at 6 months >150 μmol/L to increase the risk of allograft failure, HR 3.69 (2.10-6.48).

High serum creatinine at 6 months predicted allograft failure at 1 year in a study by Nicol et al (35). McLaren et al (98) did not find a statistically significant association between 6-month SCr and allograft failure on multivariate analysis 1.004 (1.00–1.01).

High SCr at 6 months could be the initial stages of chronic allograft nephropathy, an ill-defined process that results progressive unrelenting deterioration in allograft function (35,95).

A prospective study investigating changes in SCr over specific time intervals may be a better study so as to account for confounding factor of chronic allograft nephropathy.

5.2 Conclusion

Using binary logistic regression, we were able to answer our single specific objective.

Allograft recipients who had increased risk of having poor allograft function at one year post transplant were recipients who had;

i. Acute rejection episodes
ii. Unplanned transplant related readmissions
iii. Cyclosporine as the calcineurin inhibitor of choice
iv. Higher serum creatinine at 6 months post-transplant

Allograft recipients who had reduced risk of having poor allograft function at one year post transplant were recipient who had;

i. More urine output on post-transplant day 1

The one-year allograft survival rate was 96% and the one-year patient survival rate was 94%.

Majority of the kidney transplant recipients were at CKD G2 at one year post KTx (38.4%).

5.3 Limitations

i. The reliance of retrospective studies on records whose reliability cannot be ascertained might have resulted in chance errors by either reducing or increasing the odds. The effect of this is having significant or non-significant predictors univariate and multivariate analysis.

ii. Our sample size limited the number of covariates that we could fit in the logistic regression model e.g., dialysis vintage time, induction therapy, proteinuria, discharge SCr were not studied.

iii. This is a retrospective chart review in one facility and therefore the external validity and generalizability is uncertain.

5.4 Recommendations

i. To address the high rate of acute rejection, the cause should be determined by performing DSA and PRA tests.

ii. A prospective study should be done to identify the indications for readmission and identify interventions to improve outcomes.

iii. Tacrolimus should be the calcineurin inhibitor of choice in our transplant program.

iv. Recipients with reduced urine output in the first day of transplant should be under close surveillance and an investigated e.g. allograft ultrasound

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APPENDIX 1: DATA COLLECTION TOOL

Study proforma

Study serial number

Pre transplant variables

Recipient characteristics

1. Sex — Male ☐ / Female ☐
2. Age _____(years)
3. Body mass index — Weight (Kgs) ☐ / Height (cm) ☐ / BMI (kg/m^2) ☐
4. Date of transplant
5. Recipient comorbidities prior to transplantation

Diabetes Mellitus ☐
Hypertension ☐
HIV ☐
Glomerular disease ☐
Polycystic Kidney disease ☐
Obstructive uropathy ☐
SLE ☐
Other ☐

6. Duration of selected disease _____
7. Pretransplant residual urine output — No residual output ☐ / Residual output ☐
8. Immediate pretransplant creatinine level _____ µmol/L

9. Prior sensitization: History of pregnancy — Yes ☐
No ☐

10. Number of HLA matches _____

11. Level of education — No formal education ☐
Primary level ☐
Secondary level ☐
Tertiary level ☐

12. Marital status — Single ☐
Married ☐
Widowed ☐
Separated ☐
Divorced ☐

13. Employment status — Employed in the formal sector ☐
Self-employed ☐
Not employed ☐

Donor characteristics

1. Sex — Male ☐
Female ☐

2. Age _____

Post transplantation variables

1. Choice of calcineurin inhibitor	Tacrolimus	☐
	Cyclosporine	☐
2. Choice of antiproliferative agent	Mycophenolate mofetil	☐
	Azathioprine	☐
3. Acute rejection	Yes	☐
	No	☐
4. Delayed graft function	Yes	☐
	No	☐
5. Total urine output over 24hours (post-transplant)	Day 1 _____ mls/kg/h	
	Day 2 _____ mls/kg/h	
	Day 3 _____ mls/kg/h	
	Day 4 _____ mls/kg/h	
	Day 5 _____ mls/kg/h	
	Day 6 _____ mls/kg/h	
	Day 7 _____ mls/kg/h	
6. Total fluid input over 24hours (post-transplant)	Day 1 _____ mls	
	Day 2 _____ mls	
	Day 3 _____ mls	
	Day 4 _____ mls	
	Day 5 _____ mls	
	Day 6 _____ mls	
	Day 7 _____ mls	

7. Unplanned transplant related reoperation Yes ☐

No ☐

8. Acute kidney injury during the transplant admission Yes ☐

No ☐

9. Episode of Urinary Tract Infection Yes ☐

No ☐

10. Serum creatinine values in μmol/L At discharge _____

3 months _____

6 months _____

12 months _____

11. Post-transplant diabetes mellitus Yes ☐

No ☐

12. Post-transplant admission within 1 year Yes ☐

No ☐
If yes, total number _____

13. Opportunistic infections post-transplant

Pneumocystis Jirovecii
CMV infection
Herpes Zoster infection
Esophageal Candidiasis
Polyoma BK Virus
Tuberculosis
Toxoplasmosis
Cryptococcal infection
Other
None

14. eGFR at 12 months by MDRD-4 _____

APPENDIX 2: KNH/UoN Ethics Research Committee Approval Letter

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Ref: KNH-ERC/A/261

6th July, 2022

Dr. Evans Arnold Onyango
Reg. No. H58/32157/2019
Dept of Clinical Medicine & Therapeutics
Faculty of Health Sciences
University of Nairobi

APPROVED 06 JUL 2022

Dear Dr. Onyango,

RESEARCH PROPOSAL: PREDICTORS OF ONE-YEAR ALLOGRAFT FUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT KENYATTA NATIONAL HOSPITAL (P309/04/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P309/04/2022.** The approval period is 6th July 2022 – 5th July 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Predictors of one-year allograft function among kidney transplant recipients at Kenyatta National Hospital

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PROFESSOR MARK JOSHI

ASSOCIATE PROFESSOR / CARDIOLOGIST / CLINICAL EPIDEMIOLOGIST

DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

UNIVERSITY OF NAIROBI

SIGNED: .....DATE: 4/7/2023

PROFESSOR ERASTUS AMAYO

CHAIRMAN

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