CLINICAL PROFILES AND OUTCOMES OF KIDNEY TRANSPLANT RECIPIENTS IN KENYATTA NATIONAL HOSPITAL: A RETROSPECTIVE ANALYSIS BETWEEN 2010 AND 2019

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DECLARATION

I declare that this dissertation is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.

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To my wife and family, you are the sun that my world revolves around.

To the late Dr. A.J.O. Were, you shall never be forgotten.

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ABBREVIATIONS AND ACRONYMS

AMR	-	Antibody-Mediated Rejection
APC	-	Antigens-Presenting Cell
ATG	-	Anti-Thymocyte Globulin
BMI	-	Body Mass Index
CAN	-	Chronic Allograft Nephropathy
CKD	-	Chronic Kidney Disease
CNI	-	Calcineurin Inhibitor
CVD	-	Cardiovascular Disease
DGF	-	Delayed Graft Function
ECG	-	Electrocardiogram
eGFR	-	estimated Glomerular Filtration Rate
ESKD	-	End Stage Kidney Disease
GFR	-	Glomerular Filtration Rate
HD	-	Hemodialysis
HIV	-	Human Immunodeficiency Virus
HLA	-	Human Leucocyte Antigen
IFTA	-	Interstitial Fibrosis and Tubular Atrophy
IL2-RA	-	Interleukin-2 Receptor Antibodies
IS	-	Immunosuppression
KNH	-	Kenyatta National Hospital
KRT	-	Kidney Replacement Therapy
LRDKTs	-	Living Related Donor Kidney Transplants
MDRD	-	Modification of Diet in Renal Disease
PAD	-	Peripheral Arterial Disease
PD	-	Peritoneal Dialysis
QoL	-	Quality of Life
TB	-	Tuberculosis
UTI	-	Urinary Tract Infection

OPERATIONAL DEFINITIONS

Alive with failed allograft: A recipient whom after receiving a transplant has lost allograft function and the patient is back to dialysis. This would include recipients who had a re-transplant done thereafter as the first graft is considered lost.

Chronic kidney disease: Decreased glomerular filtration rate below the normal for a period of more than three months.

Current allograft status: The state of allograft as either functional or lost at the end of the study period

Current recipient status: The state of the kidney allograft recipient as alive with functional allograft, alive with failed allograft and back to dialysis, alive with failed allograft and re-transplanted, failed allograft and dead, died with a functional allograft

Dead with functional allograft: Deceased recipient while the allograft was still functional

Allograft survival: Estimated probability of a transplanted kidney functioning at a given time

Kidney allograft recipient: Patient who receives a donor kidney

Kidney allograft: Donated kidney for transplantation as a treatment modality for end stage kidney disease

Kidney transplantation: Surgical procedure to integrate donated kidney allograft to a recipient

Patient's survival: Estimated probability of a kidney allograft recipient being alive after transplantation

Re-transplantation: Surgical procedure to integrate donated kidney allograft to a recipient who had received another allograft previously

Short term outcomes: The clinical outcomes that occur immediately after transplantation up to one year

Long term outcomes: The clinical outcomes that occur more than one year after transplantation.

ABSTRACT

Study Background

Kidney transplant confers a significant survival advantage over long-term dialysis but overall survival is lower than age-matched controls in the general population. Negative long-term outcomes of kidney transplantation still occur even with the improved access to healthcare, medication and diagnostics. This study sought to establish the recipient clinical profiles, status of allografts after transplant and their relationships over a 10 year period.

Objective

The primary objective was to establish the clinical profiles and outcomes of kidney allograft recipients and their relationships. Secondary objectives were to establish any relationships of haemodialysis vintage, human leukocyte antigens (HLA(-A, -B and –DRB1 matches, medication used, morbidities before and after transplant with allograft outcomes.

Study design and site

This was a retrospective chart file review study on kidney transplant recipients at the KNH from 2010 to 2019.

Participants and Methods

Single-centre, retrospective cohort study involving 125 adult living related donor kidney transplants (LRDKTs) performed between January 2010 and December 2019. Files of recipients above the age of 18 years who had the kidney transplant done at the Kenyatta National Hospital (KNH) and were on follow up in the transplant clinic were included in the analysis. The data collected included the recipients' and donors' demographics, recipient clinical data including morbidities before and after transplant, HLA-A, -B, -DRB1 match, ABO blood grouping, medication used for induction and clinical status and survival of the recipients and allografts at the time of the last documented medical review. This data was collected from existing file records and entered into a study proforma.

Results

Donors were young with a mean age of 35.8±8.4 years, predominantly male at 55.2% and 84% were first degree relatives to the recipients. Donors were predominantly blood group O at 69.6% with blood group AB being the lowest recorded at 1.6%.

Recipients were young with a mean age of 39.4±11.9 years and predominantly male at 72.8%. The average body mass index (BMI) among the recipients was 21.5±3.3kg/m2. Recipients

were mostly blood group O at 60% and blood group A being 20%. Comorbid conditions documented among the recipients prior to transplant were hypertension (86.4%), diabetes (22.4%), obstructive uropathy (2.4%), chronic glomerulonephritis (37.6%) and autoimmune diseases (0.8%). The HLA matches were 11.2% at zero match, 10.4% at one match, 18.4% at two match, 23.2% at three match, 12.0% at four match, 2.4% at five match and 11.2 were haploidentical. Immunosuppresant agents used pre transplant included basiliximab in 50(40%) of recipients, tacrolimus in 32.8% and cyclosporine in 67.2% with solumedrol and prednisone used in all recipients. Post-transplant any change in calcineurin inhibitor was noted in 13(10.4%) and any change of antimetabolite was noted in 10(8%) of recipients. Post-transplant comorbid conditions included hypertension in 86.4%, diabetes of new onset after transplant in 14.4%, infections including tuberculosis noted in 11(8.8%)and cytomegalovirus disease in 15(12.0%). Acute dysfunction including acute rejection noted in 37.6, Kaposi sarcoma was documented in 3.2% of recipients and cardiovascular conditions (stroke in 1.6% and myocardial infarction in 2.4%). The estimated glomerular filtration rate (eGFR) improved from the moment of transplant and settled at the sixth month at a mean of 62.4 ml/min/1.73m^2. Allograft survival and recipient survival was 90.4% at the end of the first year, at the fifth year allograft survival was 64%and the ten year allograft survival was 37.2% respectively. Among the conditions that were associated with poor allograft survival included allograft dysfunction and tuberculosis. The use of basiliximab used in recipients who had an HLA match of less than 50% was associated with a similar survival in comparison to the recipients who did not receive it as part of their treatment while the use of cyclosporine as part of induction had better allograft survival.

Conclusion

Donors and recipients were young and predominantly male with first degree relationships and were within normal BMI limits. The recipient age, haemodialysis vintage, HLA match, pre and post-transplant comorbidity, infections and malignancy state did not impact allograft survival. There was a trend for male sex having a better allograft survival but it was not significant. The use of immunosuppressant medication impacted positively on allograft survival and reinforces the need for these medications on a long term basis. Cyclosporine was found not to be inferior on allograft survival when compared to tacrolimus. The limitation of this study was being a single centre retrospective study with limitation on retrieval of medical records that could have led to a sampling bias. It is our recommendation that the use of basiliximab be supported in kidney transplant recipients with less than 50% match as it has allograft survival similar to recipients who do not receive it due to better HLA match. We also

recommend that this LRKDT program is a viable treatment modality with improving allograft survival so the modality should be encouraged and supported.

CHAPTER ONE

1. INTRODUCTION

1.1 Background information

Kidney transplant has been the most effective treatment option for end stage kidney disease (ESKD) conferring overall mortality benefit and improved quality of life (1). Improvement in surgical techniques and improved post-operative monitoring and complications have contributed to better immediate outcomes (2).

In Kenya, the living related kidney donor transplant (LKDRT) program which is still considered "gold standard" for kidney transplantation is the only available option currently as the legal framework for deceased donor programs is pending legislation (3). The improved methods of tissue typing and the advent of less toxic immunosuppressive medications have been shown to improve the long term outcomes of kidney transplant programs around the world as more research is done into the field of transplant immunology (4). In 2014, Mwangi et al noted the one year kidney allograft survival to be above 97% and at the fourth year it was 88%in the KNH transplant program (5).

1.2 Importance of patients and allografts survival studies

With the increased number of kidney transplants, a new understanding of correlates of allograft survival and causes of death among kidney transplant recipients is needed. This is due to the growing tendency for the follow-up of kidney transplant recipients to be carried out not at transplant centres, but by general physicians and nephrologist clinics who may have limited experience with kidney transplant recipients (6).

Due to few nephrologists in the region the new information on causes of morbidity and mortality will be helpful to the many physicians outside transplant centres who are now caring for kidney transplant patients. There has been a significant reduction in the rate of mortality for this group with the major cause of mortality being attributed to cardiovascular disease (CVD). Other causes of mortality include infections, thrombosis, diabetes, high blood pressure and urinary tract infections which affect allograft survival and overall survival of the recipients (7). If these disease processes are effectively recognised and managed then the allograft and recipient survivals would significantly improve.

Major causes of allograft loss are chronic graft dysfunction or premature death with functioning allograft and allograft rejection. Non-adherence to immunosuppressive medication is the main cause of kidney allograft rejection in the first post-transplant year (6). The causes of

chronic allograft dysfunction are varied including calcineurin inhibitor toxicity, de novo or recurrent glomerular disease, and a poorly defined entity called chronic allograft nephropathy.

Many deaths among kidney transplant recipients are directly or indirectly related to immunosuppression. They include deaths due to infections and malignancies and they account for more than one third of mortality in transplant recipients (8).

1.3 Problem statement

Globally, the incidence of end stage kidney disease (ESKD) has been on the rise over the past century increasing the demand for appropriate kidney replacement therapy (KRT) including kidney transplant. According to the global burden of disease 2015 study, 1.2 million people had died from kidney failure, a 32% increase as compared to 2005 (9). CKD is estimated to affect 10% of the global population (10). Studies show that CKD is more prevalent in African countries when compared with the developed countries (6).

In Kenya, a 2006 study revealed that the prevalence of CKD in Kenya was at 15.6 per million population (6). According to the Kenya Renal Association, up to 4 million Kenyans are suffering from kidney diseases with a large proportion of this number progressing to kidney failure. As transplantation has been the treatment of choice for ESKD, the increasing number of ESKD has led to an increase in demand for kidney transplantation as a modality of KRT (8).

Despite the increased burden of ESKD, few studies have focused on kidney transplantation and specifically the clinical characteristics, recipients and allografts status in Kenya. There is an exigency for such studies, so as to help combat the CKD epidemic with more understanding of allografts and recipients' status in terms of morbidity and outcomes after transplantation.

Kenyatta National Hospital (KNH) is the largest public teaching and referral hospital in Kenya. The living related kidney donor transplant (LRKDT) program has been running in the hospital for over two decades and currently has more than 150 kidney transplant beneficiaries. Though there is partial funding from the national health insurance schemes, the medication and follow-up is largely self-funded and this has formed a point of discussion to attempt to make kidney transplant a more appealing modality of KRT in the region from a health and economic standpoint.

Despite this treatment modality being offered over more than two decades, the profiles and the short term and long term outcomes had not been reviewed. This study intended to document the clinical profiles of LRKDT recipients and their outcomes to find any relationship that could

be used to improve screening and long-term outcomes for the patients who seek this modality of KRT.

1.4 Study question

What are the clinical profiles and allograft outcomes of the kidney transplant recipients at Kenyatta National Hospital between 2010 and 2019?

1.5 Study objectives

1.5.1 Primary objective

To establish the clinical profiles and outcomes of kidney allograft recipients at the KNH between 2010 and 2019.

1.5.2 Specific objectives

i. To document selected recipients' pre-transplant characteristics including: age, sex, clinical profiles including documented causes of kidney disease, dialysis vintage and body mass index between the years 2010 and 2019.
ii. To document the selected donor characteristics including: age, sex, donor-recipient relationship, HLA-A, -B, and -DRB1 matches and ABO blood groupings between the years 2010 and 2019.
iii. To document immunosuppressive agents used and changes in medication between the years 2010 and 2019.
iv. To document morbidities post kidney transplantation in recipients from 2010 to 2019 including hypertension, diabetes, graft dysfunction, malignancies (Kaposi sarcoma) and infection (cytomegalovirus, tuberculosis)
v. To document allograft and recipients current survival status at 1, 3, 5 and 10 years defined as alive with functioning allograft, alive with failed allograft and return to dialysis, alive with failed allograft and re-transplanted, deceased after failed allograft return to dialysis, deceased with functional allograft and unknown status and graft function post-transplant by documenting functional allograft estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) formula at month 0, 3, 6, 12 and at the last clinical visit.

1.5.3 Secondary objectives

To explore relationship between patients and allograft survivals with: -

i. Haemodialysis vintage
ii. Morbidities including diabetes, hypertension, obstructive uropathy autoimmune disease and glomerulonephritis and others before and after transplantation
iii. Donors-recipients' relationships, sex, age, body mass indices and HLA-A, -B, and -DRB1 matches and donor-recipient ABO blood groups
iv. Immunosuppressive medication used pre and post-transplant.

1.6 Justification

Multiple studies have shown that kidney transplantation improves the survival of ESKD patients. Even with this improved survival, kidney allografts recipients are still highly susceptible to other morbidities after the transplantation. Another possible outcome of kidney transplantation is the rejection which may later lead to allograft loss.

This study aimed to shed light on the clinical characteristics of kidney allograft recipients before and after transplantation at the KNH. The study findings contribute to the local knowledge on allografts survival, morbidity and mortality among the recipients and may be used to better patients care.

1.7 Utility of the study

Kidney transplantation is out of reach to most patients locally. For those patients who manage to access kidney transplant programs, it is paramount to document short and long-term outcomes of these patients and their allografts. Characterization of clinical aspects which impact on the outcomes is likely to inform the strategies to better the outcomes of this modality of treatment of kidney disease.

The findings of this study can be utilized to compare the outcomes of transplantation and other modalities of treatment like haemodialysis. The findings can also inform the recruitment of prospective kidney transplant recipients on the probable expected outcomes of transplantation locally.

CHAPTER TWO

2 LITERATURE REVIEW

2.1 Chronic kidney disease and treatment modalities

Chronic kidney disease (CKD) is the decreased glomerular filtration rate (GFR) below the normal for a period of more than three months. The US National Kidney Foundation defined CKD as a GFR lower than 60 mL/min per 1·73 m² (11). CKD is classified into 5 known stages that include kidney damage with normal or increased GFR, kidney damage with mildly decreased GFR, moderately decreased GFR, severely decreased GFR and kidney failure or end stage kidney disease (ESKD) being the most advanced stage (12). At ESKD patients require KRT which can include long-term haemodialysis, kidney transplant or conservative medical approach which may be palliative according to discussion including patient preference (13). Kidney transplantation is preferred by care providers and patients due to improved quality of life when compared to chronic haemodialysis (14).

The epidemic of CKD has been projected to increase in the developing world and initial treatment being haemodialysis (HD) and peritoneal dialysis (PD) which can overstretch national resources in health, kidney transplant is seen as the treatment option of choice KTR (1). Knowing the clinical profiles of recipients and treatment options during transplant and their relationship with overall survival of allografts and kidney recipients which can then be compared with persons on other forms of therapy including HD and PD can then inform public policy and patients on the options available.

2.2 Kidney transplantation

Although organ transplant still carries its own risks, there has been improvement in the short-term management to avoid complications of organ rejection and delayed graft function (15).
Kidney transplant confers a significant survival advantage over long-term dialysis but overall survival is lower than age-matched controls in the general population. Even with the improved access to healthcare, medication and diagnostics, negative long-term outcomes of kidney transplantation still occur. Some studies have shown the main causes of the long-term kidney allograft loss as chronic rejection, recurrence of underlying disease, death with functioning allograft and acute rejection (16).

Just as in other parts of Africa, in Kenya, there is limited access to kidney transplantation due to lack of finances (17). According to the Kenya Renal Transplant Registry, the number of

kidney transplants in Kenya has been steadily increasing from under ten in the year 2006 to over 150 in 2019. This growth has been attributed to the increased uptake of transplantation as treatment modality as well as an increase in medical and therapeutic expertise in the field of kidney transplantation. After the pioneer study done by Kayima et al (3), outcomes of kidney transplantation in Kenya are not well known. Kenyatta National Hospital is one of the few hospitals in East Africa that offer kidney transplantation and is known to perform the largest number of kidney transplants in the region (6).

The success of a solid organ transplant program is important in deriving data on the long-term survival and improvement in quality of life (QoL) for people equivalent to age-matched general population (18). It has been documented that patients with ESKD have better QoL and significantly better survival rates in comparison to those on dialysis (13).

The evolution of allograft survival has improved over the last decade from all-cause mortality of 34.2 percent for living donor recipients to as high as 95 percent in 2016 from international transplant registries (19). It has also been noted that death with a functioning allograft occurs and may be attributed to better immunosuppression while also including older recipients into transplant programs (6). Allograft function assessment has also remained unchanged but the improving short and long-term outcomes are attributed to improving compliance and adherence to follow-up with improvement in tolerance to immunosuppressive medications (20).

Survival of kidney transplant recipients matched with patients who are on preparation awaiting transplant is the only true way of assessment as comparison done with dialysis patients brings in confounders. These confounders include a generally older population on dialysis with more co-morbidities and who may not qualify for transplant (21). From the United States Renal Data System (USRDS) a survival analysis performed on over 220,000 dialysis patients reported over 20,000 of patients who underwent transplant had an annual death rate that was lower than patients on waiting lists (3.8 versus 6.3 per one hundred patient-years). Also noted was improved survival for diabetics, African Americans in any age group including those above age 65 years (22).

In Africa, Kenya is one of the 12 countries performing kidney transplants relying on living donors which has its limitations in the social setting (1). The first kidney transplant in Kenya was done in 1978 on a ten-year-old girl using a deceased donor organ (3). Since then, few studies have been done to assess the transplant progress. In the pioneer study done by Kayima

et al in 1996 fifteen living donor recipients were assessed over a minimum of twenty-four-month period. It was noted that at the end of one year, one patient had returned to dialysis after a failed graft, three recipients died, two of whom died in the first year and the third died after 23 months (18). Some of the barriers to transplant programs include the evolving epidemics of non-communicable diseases like diabetes and increase in communicable diseases like human immunodeficiency virus (HIV) and tuberculosis (TB) (23). These diseases have to be included in the preparation phase of the transplant recipients and can easily delay or disqualify donors and recipients from the transplant process (24).

There is paucity of data on the current allograft and recipient survivals and possible contributors to improving these factors in Kenya (3,5). The knowledge of these contributors to negative or positive outcomes can be used to improve screening of donor-recipient pairs to improve the outcomes and quality of life as well as improve confidence for other health institutions that may be interested in initiating their own kidney transplant programs and increase overall access to kidney transplant services.

2.3 HLA-A, B, and DRB1 matches between the kidney allografts donors and recipients

The compatibility of HLA between donor and recipient plays a major role in the survival of the allografts. The HLA matching between the allograft donor and recipient has been known to improve the result of kidney transplants (25). Cases where there are no mismatches between donor allografts and any of the recipient's loci of the HLA-A, B, and DRB1 show best outcomes of the transplant. Studies have shown that relative risk of allograft failure being weakly associated with the number of antigens mismatches at HLA-DRB1 (26).

Once transplantation has been done the immune system response is directed against mismatched HLA that is expressed on the donor's kidney. In patients who have developed HLA-specific antibodies due to previous exposure to HLA alloantigen, HLA matching is very important. This is because these patients are highly sensitized and any mismatches could cause allograft rejection (26).

2.3.1.1 Induction and maintenance immunosuppressive regimens in the kidney allografts recipients

Immunosuppression (IS) is administered to kidney transplant recipients to prevent rejection episodes and loss of the renal allograft. In 1960, the first successful kidney transplantation with immunosuppressive drug regimens was achieved. The immunosuppressive agents included azathioprine, prednisone, and often polyclonal antibodies to lymphocytes administered immediately after transplantation. Since then, the optimal regime has not been established and

different kidney transplant centres use different regimens. However, most centres rely on a triple IS after induction with either interleukin-2 receptor antibodies (IL2-RA) or anti-thymocyte globulin (ATG). Immunosuppressive management is important in the management of complications such as malignancies, diabetes, infections and other special situations (27).

The induction therapy is administered pre-transplantation, during or after kidney transplantation where two drugs are mainly used. These drugs include the IL2-RA basiliximab and ATG. A number of clinical studies highlighted the use of induction therapy in combination with standard maintenance. Studies have shown evidence that it is superior in reducing kidney allograft rejection and allograft failure when compared to standard maintenance therapy alone (28).

2.4 Outcomes of kidney transplantation

With the continuance of research in kidney transplantation and advancement in immunosuppressant medication, surgical and monitoring protocols, the outcomes of kidney transplants have overall improved. Allograft outcomes include either continued allograft survival or loss of graft through allograft rejection, allograft failure, de-novo kidney disease, recurrence of primary kidney disease (such as focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis and diabetic nephropathy) and death of a recipient with a functioning allograft. Recipient outcomes may be categorised as living and deceased with a functional or non-functional allograft respectively (29).

2.5.3 Short term outcomes

Recipient and allograft outcomes that can result in loss of allograft function within the first year post-transplant with causes including allograft dysfunction due to: acute rejection; de-novo disease; recurrence of primary disease; vascular or urological causes; infections and for the recipients: new onset cardiovascular diseases; malignancies; organ system diseases from liver, neurological and skin and all-cause mortality (14). After transplantation, the recipients are monitored closely to detect any early signs of allograft dysfunction. The most common negative early outcome of kidney transplantation is the delayed graft function (DGF) (2).

2.5.3 Long term outcomes

After the first year post-transplant chronic allograft nephropathy; diabetes post-transplant; infections; malignancies; organ system diseases; recurrence of primary kidney disease; allografts and recipients survival are considered as long-term outcomes (14,16). The long-term success of the new kidney transplant depends on the surgery, perioperative and post-operative

management. Studies have shown the survival of allografts has improved over the years with long-term outcomes being influenced by donors' and recipients' factors including compliance to medication. Negative long-term outcome may be lessened by early management and amelioration of risk factors in the immediate postoperative period (30).

2.5.3 Allograft survival

Allograft survival is defined as the time after transplant and allograft failure specified as either the return to dialysis or re-transplantation (31) and is determined by the period of time the recipient uses the transplanted kidney before censoring either by death of the patient or allograft loss due to dysfunction. Some morbidities that affect the kidney allograft recipient might lead to the allograft loss (16). Some of the causes of acute allograft loss include non-perfusion due to complications such hyper acute, acute, or accelerated vascular rejection or because of thrombosis. Allograft rejection can be classified in reference to the time of occurrence post transplantation as hyper acute which occurs from minutes to three days, acute rejection which occurs from three days to six months and chronic allograft nephropathy which occurs beyond the sixth month after transplantation (29).

2.5.3 Recipient survival

In recent studies the duration of time between last kidney transplant and recorded death has been used as a definition and has been increasing due to the improvements in screening, surgical technique, immunosuppressive medication, and follow-up. In Kenya, the survival at one year of over 90% was noted in the study by Kayima et al in the early 1990's (3) and this improved to 97% in the study done by Mwangi et al in 2014 (5). This compares to other studies in the developed world with survival rates above 90% at the first year (32,33). Mortality may occur in the presence of a failed allograft and in other cases due to factors other than kidney disease hence the patient dying with a functioning allograft (34).

2.5.3 Dead with functional allograft

Death of the recipient with functional graft after allograft transplant is one of the major causes of allograft loss and is defined as a kidney allograft recipient who had a preserved kidney function without need of renal replacement therapy (HD or PD) (34).

2.5.3 Alive with failed allograft

This is a situation where the kidney allograft becomes non-functional and the recipient is put on other modalities of KRT. In the event of a failed allograft, the recipient either goes back to dialysis or has another transplant. Allograft loss has reduced over the years, with the new

immunosuppressant's and continuance in kidney transplantation knowledge but has not been completely eradicated (34).

2.5.3 Return to dialysis

After transplantation, most patients go back to stage 2 or stage 3 of CKD. Patients with failed allografts may also choose to return to dialysis although the mortality rate among this group has been shown to be higher than those who have not yet had the transplant (35).

2.5.3 Re-transplantation

Re-transplantation is an option that is done after a failure of the allograft. Previous kidney transplants provide insight on the barriers to the next transplant. It is important to examine physical and immunological aspects of re-transplantation as it is less successful than the previous transplant. Re-transplantation success rate is less especially if the first graft is lost within 3 months due to acute rejection. Immunological reactivity and selection of another donor should be carefully examined keeping in mind that immune allo-sensitization has been documented to be the major reason for reduced outcomes after the primary transplantation (35).

2.5 Morbidities among the kidney allograft recipients before and after kidney transplantation

1.1.1 Morbidities before kidney transplantation

The assessment of patients for transplant requires an in depth medical and surgical history including a history of blood transfusions. Obesity, diabetes and high blood pressure are among the factors that should be taken into account as studies show an increase in graft rejection among these groups (14). Increased body mass index (BMI) among the obese poses as a threat during surgery with an increased risk of wound complications, poor healing, post-transplant diabetes, and also increased mortality (36).

In developed countries and many developing countries, diabetes and hypertension are the leading causes of CKD (37). These two conditions increase the progression of CKD and the risks of complications arising from kidney diseases. CVD in ESKD patients is a major cause of mortality responsible for 50% of the deaths among CKD patients (12).

Different types of morbidities before the transplant determine the appropriateness of the transplant, fitness of the recipient and the success of the transplant if conducted. Some of these conditions would exacerbate in the event of surgery or the administration of immunosuppressant medication. Identification of these conditions that may worsen the

allografts and recipients survival after kidney transplant is important when evaluating the risk-benefit of performing the kidney transplant (38). Morbidities that should be carefully considered before transplantation are viral infections with human immunodeficiency virus (HIV), hepatitis B and hepatitis C, cytomegalovirus and in some centres the herpes virus and Epstein Bar virus (19).

1.1.2 Morbidity after kidney transplant

Kidney transplant provides long-term survival benefits as compared to CKD patients under dialysis but the complications that occur after the transplantation can lower the survival. Studies show an increase in mortality just immediately after the transplant compared to the non-transplanted patients undergoing haemodialysis is increased exponentially within the first few months post-transplant (39). The common complications are post-transplant diabetes, allograft dysfunction, vascular complications, chronic allograft nephropathy, urological complications, arterial thrombosis, renal vein thrombosis, postoperative bleeding, acute rejection, graft loss, among many others (40). Recipients and donors should be educated on the possible risks and complications that may occur as a result of the transplantation. Anticipating the possible complications that would arise after the transplant surgery and the approach to standardised treatment is vital before the surgery. Protocol guided regular diagnostic evaluation after the surgery increases survival as the allograft recipient receives timely diagnosis and treatment for morbidity that could compromise the patient and allograft survival.

2.5.3 Cardiovascular complications after kidney transplantation

Even before kidney transplantation, ESKD patients are at a greater prevalence of having CVD compared to the overall population. The risk of death in ESKD patients is also relatively high even when adjusting for other confounding variables such as age, diabetes and heredity among other risk factors. This risk significantly reduces after kidney transplantation compared to when the CKD patient is on dialysis (41). Cardiovascular disease has been said to be the leading cause of mortality in allograft recipients with functioning grafts hence it is also the leading cause of allograft failure (12).

Cardiovascular complications that occur after kidney transplantation include thrombotic and haemorrhagic strokes, peripheral arterial disease (PAD) and heart disease. Ischemic heart disease is the major cause of heart disease and mortality after kidney transplant although other heart diseases like structural heart disease can also cause mortality after kidney transplant. Structural heart disease is majorly caused by hypertension after kidney transplant. The risk factors for CVD after kidney transplants include age, diabetes, smoking, years after transplant, serum albumin, splenectomy and sex (40).

2.5.4 Infections in kidney transplant recipients

Management of infections in kidney transplantation is important as the consequences of these infections maybe allograft failure or mortality. Different factors that are related to immune function complicate the management of infections in kidney transplant recipients. The immune system of the recipient and epidemiology of infection influence the successful management of infections. Transplant recipients are susceptible to a large number of infectious pathogens, present diminished signs and symptoms of infection. Transplant recipients may develop systemic signs (e.g., fever) in response to non-infectious processes (e.g., graft rejection, drug toxicity) with multiple processes often present. Patients who are immunocompromised fight infection poorly with high morbidity and mortality which create the urgency for an early and specific diagnosis for antimicrobial therapy (42).

Major infections which can cause allograft dysfunction and may be fatal include viruses like cytomegalovirus (CMV), BK virus, Herpes simplex, varicella zoster and Human Herpes virus 8 in Karposi sarcoma (8). Most kidney transplant recipients have the T lymphocyte dysfunction as a result of immunosuppression which makes them more susceptible to viral infections. The viral infections contribute to graft dysfunction, graft rejection, and systemic illness. The recipient with these viral infections is also at a heightened risk for other opportunistic infections (e.g., *Pneumocystis* and *Aspergillus*) and virally-mediated cancers (34).

The risk of infection in a kidney transplant recipient is determined by the interaction of two key factors. The two key factors include epidemiological exposures of the patient and the net state of patient's immunosuppression. The epidemiological exposures can be categorized into donor-derived infections, recipient-derived infections, community-derived exposures and nosocomial exposures.

2.6 Recipients and allograft survival and causes of mortality

Earlier in the 1970s, patient survival with a functioning kidney was reported at 50% at one year. Most of the patients experience one or more acute rejection in the first year after the transplant (43). The adoption of cyclosporine in the 1980s improved this situation but did not eliminate allograft rejection as the major cause of allograft loss. In the 1990s, remarkable improvement was seen with an increased allograft survival being observed in the first year after transplantation. This improvement was attributed to the new immunosuppressive drug regimens. Despite the high risk for allograft failure among kidney transplant candidates, one-year allograft survival exceeding 90% is now common (43). This has shifted the focus from preventing short-term rejection to maintaining long-term patient and allograft survival. Improvements in outcomes for patients who survive beyond the first year with a functioning kidney have not been as dramatic as improvements in short-term outcomes (43).

A study conducted in Kenya in 2003 on kidney transplant recipients found the patient survival was at 77.8% during the one-year after transplant and 63.1% five years after transplant. The study found the overall mortality rate being at 37.8%. Allograft survival after one year of transplant was found to be 77.8% and 52.7% five years after transplant (33).

CHAPTER THREE

3 METHODOLOGY

3.1 Study design

This was a longitudinal retrospective study

3.2 Study site

The Kenyatta National Hospital (KNH) is a tertiary referral hospital located in Nairobi, the capital city of Kenya in East Africa. KNH was established in 1900 with a bed capacity of approximately 2000 beds and serves as the teaching hospital for the University of Nairobi, Faculty of Health Sciences, for the undergraduate, post graduate programs and fellowship programs. It serves as a referral hospital for Kenya and East Africa. The KNH kidney transplant program is currently a living donor transplant program with 200 kidney transplants over the 10-year period between 2010 and 2019

3.3 Study duration

The study was performed over a period of four months in July to October 2021.

3.4 Study population

All adult transplant recipients who underwent kidney allograft transplantation in KNH between 2010 and 2019

3.5 Case definition

Any adult patient who received kidney allograft for treatment of ESKD in KNH between 2010 and 2019

3.6 Inclusion and exclusion criteria

3.6.1 Inclusion criteria

Adult patients above the age of 18 years with end stage kidney disease that were evaluated for suitability for kidney transplantation and received the allograft transplantation at the Kenyatta National Hospital between 2010 and 2019.

3.6.2 Exclusion criteria

Any patients who are below the age of 18 years or who were not transplanted at Kenyatta National Hospital even if they are on follow up at KNH.

Any patients who were lost up to follow up immediately after transplantation and thus the follow up medical records are not available shall be excluded from the study.

3.7 Sample size determination

This will be a finite population and census will be carried out in all the patients. The minimum number of the patients who must be recruited will be calculated using the formula by Daniels 1999 with finite correction.

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

where n' = Sample size with finite population correction,
N = Population size,
Z = Z statistic for a level of confidence,
P = Expected proportion (If the prevalence is 20%, $P = 0.2$), and
d = Precision (If the precision is 5%, then $d = 0.05$)

Where, N =168, Z = 1.96, and P = 50%,

At least 117 (n') kidney transplant recipients were considered as the minimum number of the patients required for this population study.

3.8 Recruitment of study subjects

All available medical records of patients who underwent kidney transplants at KNH were retrieved and perused for eligibility. A study proforma **(Appendix 1)** was given a serial number that was used to ensure privacy of the individual so that no name appears on any document. Demographic data was recorded and the allograft and recipient's current status as outcome. Kidney allograft outcomes were either functional or lost allograft. A recipient was considered to have functional allograft if alive and the allograft was working without need of renal replacement therapy. A recipient was considered to have lost allograft if the recipient died with working allograft, if the allograft failed and the patient re-transplanted and if the allograft failed with the recipient requiring renal replacement therapy of dialysis.

The other details recorded were the documented morbidities before and after transplant, the duration of dialysis, age at transplantation, donor's age and sex, HLA-A, -B, -DRB1 and DQB1 genes and alleles as well as matches and blood groups for the donors and recipients, The recipient's follow up serum creatinine, immunosuppression medications and other parameters were recorded at least immediately after transplant at discharge from hospital, three months, six months, one year and the last documented visit. The modification of diet in renal disease (MDRD) formula was used to calculate eGFR at these different times.

3.9 Data management

3.9.1 Data collection, storage, and cleaning

Completion of the study proforma was verified prior to the principal investigator/research assistant returning files to the medical records. The filled study proformas was kept in a lockable cabinet only accessible by the investigator. Data collected was uploaded to a password protected Microsoft excel for cleaning that was accessible to the principal investigator.

The data was entered into a pre-programed format in the Statistical Package for the Social Sciences (SPSS) version 21.0. Data cleaning was done before analysis. A back up of the data was done on an external drive with access to the backups limited to the principal investigator only.

3.9.2 Data analyses

Continuous variables like age had the means and standard deviations calculated if normally distributed or median if skewed. Student t-test was used to test for significance. Categorical data like immunosuppressant regime, HLA-A, B, and DRB1 matches, diabetes disease, cardiovascular disease, hypertension had the frequencies and proportions calculated. Chi square test was used to test for significance of the categorical data. The survival analysis for the patients and allografts was performed using Kaplan Meier survival analyses. All analyses were done at 95% confidence with p-value <0.05% considered significant. Results were presented to the renal unit consultants and recipients upon review.

3.9.3 Quality control

To ensure that the documentation is done correctly study proformas were picked at random and checked by the principal investigator for correct entry of information each day. All the filled study proforma was checked for completeness before the medical records were returned for filing. Filled proformas were serialized to enable cross checking for the correct entry into the computer spreadsheet. A data entry clerk proficient in computer packages was hired to enter the data. Random checks at the entered data were done by the principal investigator by picking proforma and countercheck whether the data entered was correct.

3.10 Ethical considerations

3.10.1 Approvals

Before the commencement of the study the proposal was presented to the faculty in the East African Kidney Institute for approval. After this approval the proposal, ethical clearance from

the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC) was sought and approved under reference KNH-ERC/A/279.
After the KNH-UoN ERC approval, authority to use the medical records in KNH was received from KNH and from the Medical Record In-Charge in KNH.

3.10.2 Privacy and confidentiality

Confidentiality of the data collected was upheld and the information collected was securely stored and only accessible to the investigators. Coding was done to protect privacy so that no names of patients appear on any document.

CHAPTER FOUR

4 RESULTS

2.7 Study recruitment

Out of the 168 kidney eligible transplants done, a total of 142 kidney allograft donor-recipient pairs medical files were available and were screened for eligibility to the study over a two-month period from September to October 2021. Seventeen files were excluded due to various reasons. One hundred and twenty-five files were eligible for the study (figure 4.1) with more than 50% representation per year, distributed between the year 2010 and 2019 (Table 1).

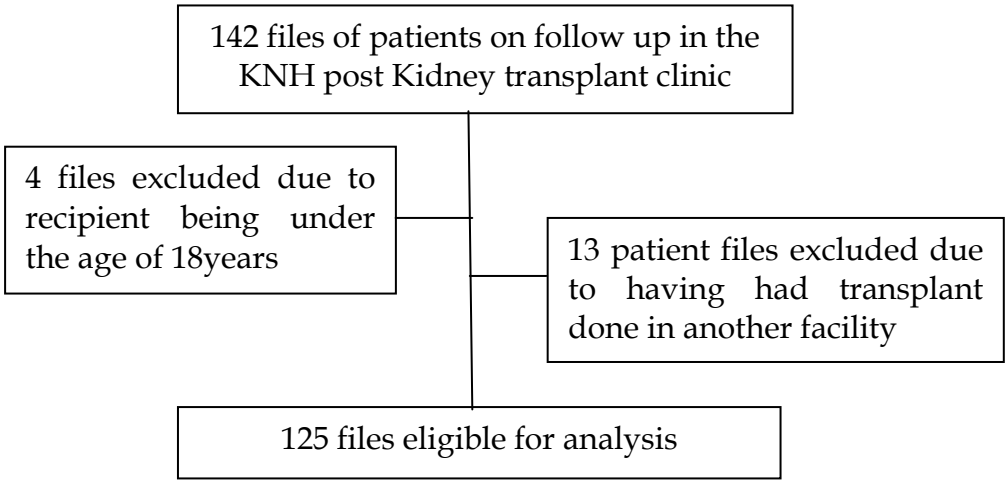

Figure 4.1: Recruitment flowchart

Table 1 Eligible kidney allograft recipients' distribution by year of transplantation

Year of transplantation	Number of recipient files collected (%)	Number of eligible transplants done	Percentage representation (%)
2010	20 (16)	25	80.0
2011	16 (7.2)	23	69.6
2012	9 (7.2)	17	52.9
2013	9 (7.2)	18	50.0
2014	18 (14.4)	23	78.3
2015	11 (8.8)	15	73.3
2016	7 (5.6)	8	87.5
2017	7 (5.6)	8	87.5
2018	10 (8)	12	83.3
2019	18 (14.4)	19	94.7
Total	**125 (100.0)**	**168**	

2.8 Kidney allograft donor sociodemographic characteristics

The mean age of donors was 35.8 ± 8.4 years with a marginal male predominance of 55.2% (69). Most were First degree relatives 105 (84%). Almost seven in every ten donors had blood group "O" (Table 2).

Table 2: Kidney allograft donor characteristics

Characteristic	Description	
Age (year)	Mean ±SD	35.8 ±8.4
Sex		**Number (%)**
	Male	69 (55.2)
	Female	56 (44.8)
Donor to recipient relationship		
	First degree relatives	105(84)
	Second degree relatives	20(16)
ABO blood group		
	O	87(69.6)
	A	24(19.2)
	B	12(9.6)
	AB	2(1.6)

2.9 Kidney allograft recipients sociodemographic and clinical characteristics

The recipients were predominantly male 91(72.8%), with a mean age at transplantation of 39.4 ± 11.9 years and median haemodialysis vintage of 18 months. Most recipients (64%) had a body mass index (BMI) within normal limits of 21.5 ± 3.3 Kg/m^2. The commonest documented morbidities before kidney allograft transplant were hypertension, chronic glomerulonephritis and diabetes in 86.4, 37.6% and 23.2% respectively. Post-transplant diabetes was noted in 18(14.4%) of recipients. Tuberculosis was diagnosed in 8.8% recipients and probable or confirmed diagnosis of CMV in 15(12%). Four (3.2%) recipients suffered from Kaposi sarcoma and none from post-transplant lymphoproliferative disorder. Among other conditions documented, cardiovascular morbidities that were significant, was stroke in 2(1.6%) and myocardial infarction 3(2.4%) of the recipients (Table 3).

Table 3: Kidney allograft recipients' sociodemographic and clinical characteristics

Characteristic		Description
Age at transplantation (year)	Mean ±SD	39.4±11.9
Haemodialysis vintage	Median (IQR)	18.0 (11.5-28.5)
BMI (kg/m2)	Mean ±SD	21.5±3.3
BMI category		**Number (%)**
	Underweight (BMI <18.5 kg/m^2)	22(17.6)
	Normal (BMI 18.5-24.9 kg/m^2)	81(64.8)
	Overweight (BMI 25-29.9 kg/m^2)	20(16.0)
	Obese (BMI >30 kg/m^2)	2(1.6)
Sex		
	Male	91(72.8)
	Female	34(27.2)
Documented comorbidity before transplant		
	Diabetes	28(22.4)
	Hypertension	108(86.4)
	Autoimmune and Chronic glomerulonephritis	48(38.4)
	Obstructive uropathy	3(2.4)
	Others	21(36.0)
Documented comorbidity after transplant		
	Diabetes	46(36.8)
	Hypertension	108(86.4)
	Obstructive uropathy	1(0.8)
	Glomerulonephritis	3(2.4)
	Tuberculosis	11(8.8)
	Cytomegalovirus	15(12.0)
	Kaposi sarcoma	4(3.2)
	Allograft dysfunction (acute or chronic rejection)	47(37.6)
	Others	41(32.8)
	Stroke	2(1.6)
	Myocardial infarction	3(2.4)

Recipients, like the donors, were predominantly blood group "O" in 75(60%). A human leucocyte antigen (HLA)-A and DRB1 match above 3/6 was found in 60% and 23.2 recipients had a 50% match. A single match at HLA-A, HLA-B and HLA-DRB1 was found in nearly two out of every five recipients. Among medication used for induction and maintenance, basiliximab was used in 50(40%) of recipients who had HLA match of less than 50%. Cyclosporine was used in more recipients than tacrolimus over the ten year review (67% versus 32.8% respectively) as shown in Table 4.

Table 4: Kidney allograft recipients' blood group, HLA match and induction medication

Characteristic	Number (%)
Recipient ABO blood group	
O	75(60.0)
A	25(20.0)
B	17(13.6)
AB	8(6.4)
Donor-recipient HLA- A, -B, DRB1 match	
Zero match at HLA-A first and second loci	35(28)
One match at HLA-A first and second loci	52(41.6)
Two match at HLA-A first and second loci	38(30.4)
Donor-recipient HLA-B	
Zero match at HLA-B first and second loci	32(25.6)
One match at HLA-B first and second loci	56(44.8)
Two match at HLA-B first and second loci	37(29.6)
Donor-recipient HLA-DRB1 match	
Zero match at HLA-DRB1 first and second loci	34(27.2)
One match at HLA-DRB1 first and second loci	52(41.6)
Two match at HLA-DRB1 first and second loci	39(31.2)
Donor and recipient HLA-A, -B and –DRB1 match of 6 antigens	
Zero match	14(11.2)
One match	13(10.4)
Two matches	23(18.4)
Three matches	29(23.2)
Four matches	15(12.0)
Five matches	3(2.4)
Six matches	14(11.2)
Medication used Pre-transplant for induction and maintenance[α]	**Number (%)**
Induction with basiliximab	50(40.0)
Tacrolimus	41(32.8)
Cyclosporine	84(67.2)
Soulmedrol	125(100.0)
Prednisone	125(100.0)
Change of immunosuppressant medication	
Any change of calcineurin inhibitor	13(10.4)
Any change of antimetabolite	10(8)

2.10 Kidney allograft function in the first, third, sixth, twelve month and during the last review after transplant

Tracking the kidney allograft function using estimated glomerular filtration rate (eGRFR) by utilizing serum creatinine and Modification of Diet in Renal Disease (MDRD) formula at the first, third, sixth and twelfth month is shown in table 5.

Table 5 Estimated glomerular filtration rates at selected time intervals

Time interval	Mean eGFR ± SD (ml/min/1.73m2)
First month	26.6±16.8
Third month	61.2±21.4
Sixth month	62.4±22.3
Twelve month	62.4±22.7

The allograft function as per KDIGO grades by eGFR at different times demonstrating that recipients tended to stabilise at grade 2 at 12 months (table 6).

Table 6 Allograft function grading as per KDIGO using eGFR calculated using modification for diet in renal disease (MDRD) formula

eGFR (ml/min/1.73m²)	First Month n (%)	Third month n (%)	Sixth month n (%)	One year n (%)
eGFR < 15	28 (22.6)	5(4.1)	5(4.2)	6(5.1)
eGFR 15-29	55(43.5)	6(5.0)	2(1.7)	3(2.5)
eGfr 30-44	21 (16.9)	10(8.3)	9(7.6)	9(7.6)
eGfr 45-59	14 (11.3)	29(24.0)	37(31.1)	28(23.7)
eGfr 60-89	5 (4.0)	63(52.1)	52(43.7)	62(52.5)
eGfr>=90	1 (0.8)	8(6.6)	14(11.8)	10(8.5)
Total n(%)	124	121	119	118

eGFR estimated glomerular filtration rate

2.11 Kidney allograft and recipients outcomes

Kidney allograft outcomes were either functional or lost allograft. A recipient was considered to have functional allograft if alive and the allograft was working without need of renal replacement therapy. A recipient was considered to have lost allograft if the recipient died with working allograft, if the allograft failed and the patient re-transplanted and if the allograft failed with the recipient requiring renal replacement therapy of dialysis. By the end of this study in October 2021, for the 125 recipients who

were transplanted between 2010 and 2019 at KNH, 76(60.8%) had functional allograft (alive with functional allograft) while 49(39.2%) had lost their allografts. For the 49 recipients who had lost their allograft, 22(44.9%) died while their allograft was still functional, 13(26.5%) had failed allograft back to dialysis and died, 13(26.5%) were alive with failed allograft and were dependent on dialysis while one patient had the first allograft failure and was re-transplanted. (Table 7)

Recipient outcomes were either alive or deceased. A recipient was considered alive if from the recent medical records (≤24 months); the recipient was alive with or without a functional allograft. The recipient was considered deceased if there was documentation of death or if the recipient had missed clinic for more than two years. For the 125 kidney allograft recipients, 90(72.0%) were alive. Out of the 90 recipients who were alive, 76(84.4%) were alive with functional allograft, 13(14.4%) were alive with failed allograft and back to dialysis while one (1.1%) had re-transplanted (Table 4.7).

Table 7 Recipients and allograft outcomes

Description		Number (%)
Functional allograft	76(60.8)	
Recipient alive with functional allograft		76(60.8)
Lost allograft	49(39.2)	
Alive failed graft back to dialysis		13(10.4)
Re-transplanted		1(0.8)
Died with functional allograft		22(17.6)
Died after loss of allograft		13(10.4)

For the recipients with functional allografts, the longest has lived for 139 months and the shortest survival time was 24 months. For the recipients who lost their kidney allografts, the longest had lived for 118 months while the shortest had lived for 24 months since transplantation. The age and dialysis vintages were similar between the two groups. There was a trend toward male sex having longer allograft survival but it was not significant (p-value of 0.093). Post-transplant diabetes did not significantly impact allograft survival. HLA match done for nil, single or full match between donor and recipient at HLA-A, HLA-B and HLA-DRB1 was found to not be significant on the allograft survival. Recipients having developed Kaposi Sarcoma or an infection of TB or CMV had near equal numbers of functional allograft versus lost allograft though it

was not found to be significant. Comparison between recipients who had functional allografts and those who had failed allografts shows that duration since transplantation, induction with basiliximab, induction with tacrolimus and induction with cyclosporine were significant as shown in table 8.

Table 8 Comparison between the recipients with functional and lost allograft

Characteristic	Functional allograft (n=76)	Lost allograft (n=49)	p-value†
Age(year) Mean ± SD	39.5±11.9	39.3±12.2	0.899
Dialysis vintage (month)			0.328
Median (IQR)	18.0(12.0-30.0)	14.0(10.0-24.0)	
Duration since transplant (month)			**0.002**
Median (IQR)	53.0(29.0-90.0)	32.0(13.5-60.0)	
Sex			0.093
Male n(%)	55(72.4)	36(73.5)	
Female n(%)	21(27.6)	13(26.5)	
Diabetes before transplant n(%)	20(26.6)	8(16.3)	0.193
Diabetes after transplant n(%)	31(40.8)	15(30.6)	0.251
HLA-A match			0.164
Zero n(%)	24(31.6)	11(22.4)	
One n(%)	32(42.1)	20(40.8)	
Two n(%)	20(26.3)	18(36.7)	
HLA-B match			0.140
Zero n(%)	23(30.3)	9(18.4)	
One n(%)	33(43.4)	23(46.9)	
Two n(%)	20(26.3)	17(34.7)	
HLA-DRB1 match			0.222
Zero n(%)	22(28.9)	12(24.5)	
One n(%)	34(44.7)	18(36.7)	
Two n(%)	20(26.3)	19(38.8)	
Medication Used on Induction and maintenance			
Induction with basiliximab n(%)	36(47.4)	14(28.6)	**0.037**
Tacrolimus n(%)	31(40.8)	10(20.4)	**0.018**
Cyclosporine n(%)	45(59.2)	39(79.6)	**0.018**
Infections and Malignancy post-transplant			
Tuberculosis infection n(%)	6(7.9)	5(10.2)	0.658
Cytomegalovirus n(%)	8(10.5)	7(14.3)	0.529
Kaposi sarcoma n(%)	2(2.6)	2(4.1)	0.654

†Mann-Whitney Test for comparison between the two groups, Grouping Variable: Kidney allograft outcome as at 2021 October, HLA human leucocyte antigen, IQR interquartile range, n number

At one year survival of the graft was 91.4% then declined to 64% at five years with 37.2% of recipients alive with functional allografts at 10 years as shown in the Kaplan Meier curve in fig 4.2.

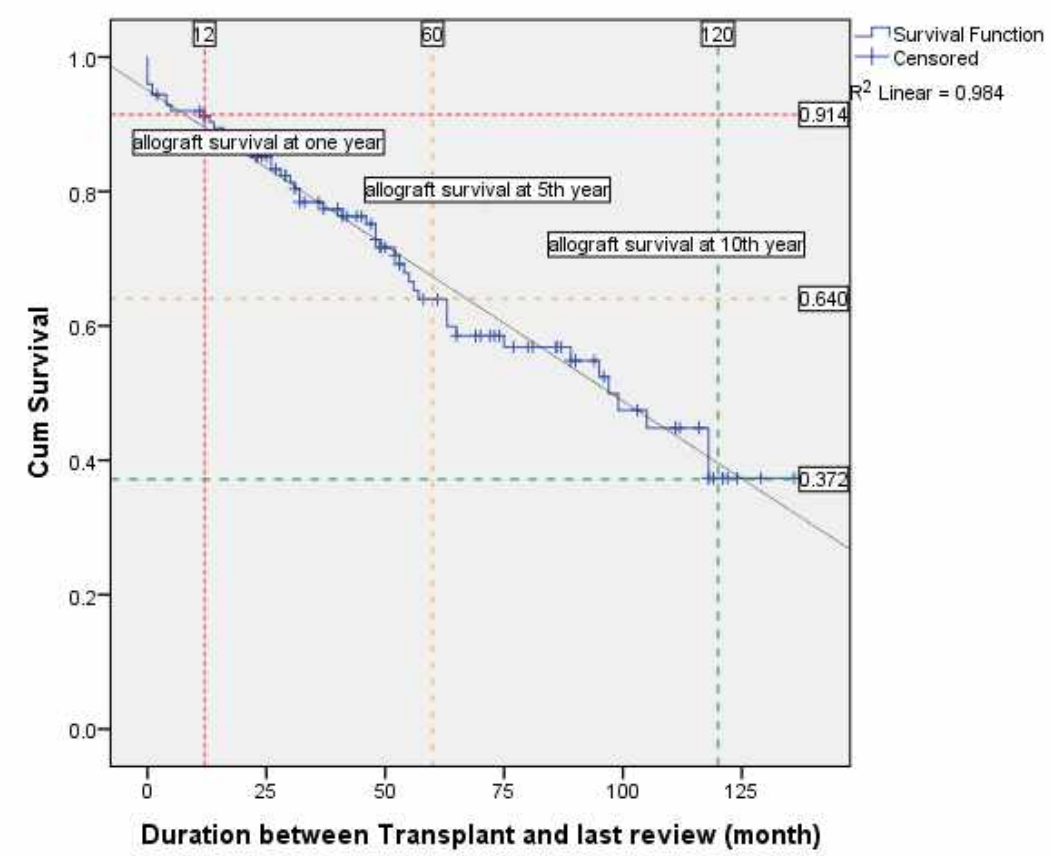

Figure 4.2. Aggregate allograft survival

Basiliximab was used in patients with HLA match less than 50% which was significant as it made survival follow a similar pattern to those who did not receive it as part of induction (fig 4.3).

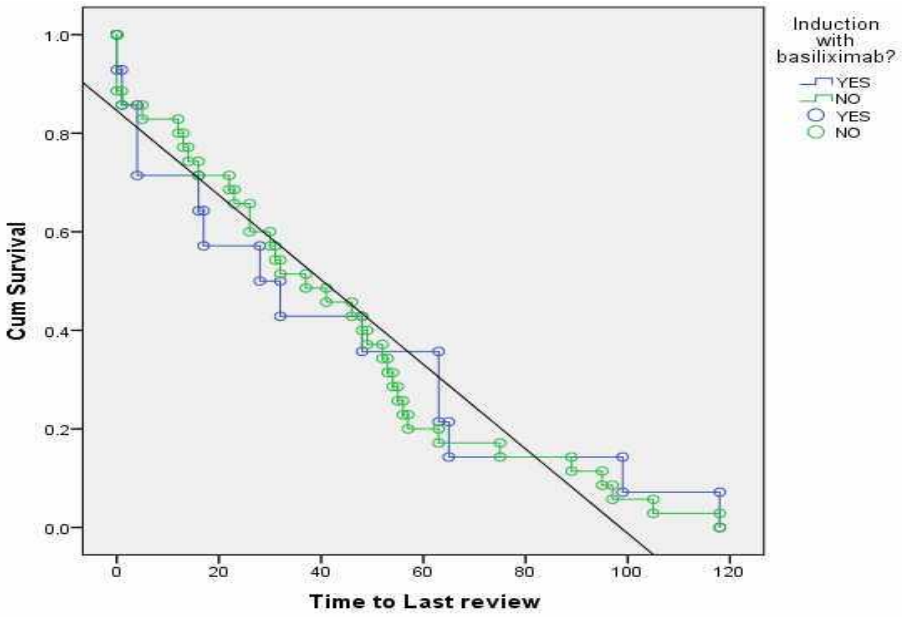

Figure 4.3. Differential allograft survival by induction with or without Basiliximab

On comparison of cacineurin inhibitors used as part of induction cyclosporine was shown to have a significant effect on recipients.

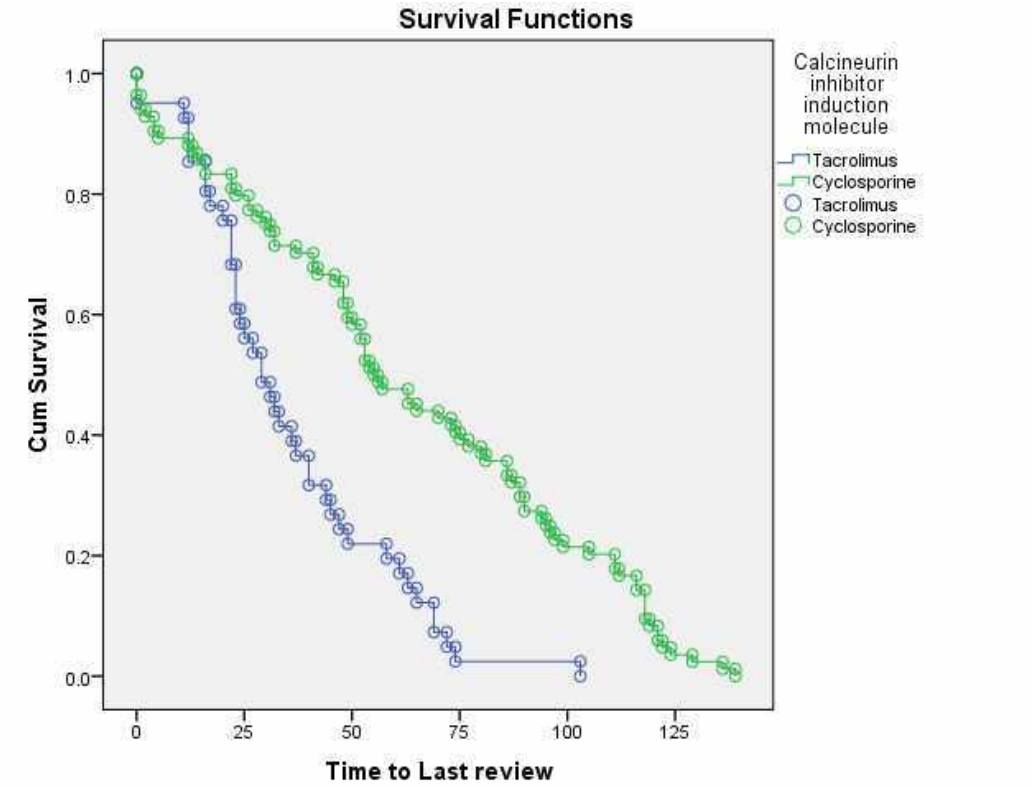

Figure 4.4 Differential allograft survival by induction with tacrolimus and cyclosporine

CHAPTER FIVE

3 DISCUSSION

Kidney transplant is an effective treatment option for end stage kidney failure. Over the last two decades the uptake of transplant in Kenya has improved with more than two hundred successful kidney transplants over the last decade alone. Although the numbers are much lower than the more developed nations, a steady increase in uptake of this modality of treatment has been noted with recipients continuing on to have better quality of life and return to regular activities of daily living and essential productivity.

Clinical profiles

Donors

We found that living donors in our population to be young with a mean age of 33.9 years with more male donors. This is similar to studies done in Kenya (3,5) and the United Network for Organ Sharing (UNOS) (44) but differs with other parts of Africa like South Africa (45) and Egypt which are similar to donor population in Brazil that had young female donors (46). First degree relatives and specifically siblings are the majority of donors (80%) in this study as was seen in the study done by Kayima et al in 1996 (3). With some kidney disease having genetic and familial tendencies these donors who were of excellent health while being chosen would have to be followed up in order to see if there will be donors who would require dialysis in the future. Living-related Kidney donation has its inherent risks of surgical procedure as well as immediate change of health status of the donors who have a reduction in eGFR and possible undesirable effects on long term survival (56). Our donors are mostly blood group O (69.6%) who would also be needed as universal blood donors. These factors may be supporting a need for a deceased organ donor program that may help to mitigate these risks and widen the potential donor eligibility and increase uptake in kidney transplant. There are significant strides forward in implantable bio-artificial kidney (57) and xenograft science (58).

Recipients

The mean age of recipients was 39.4 years with more male recipients. This age group represents the peak productivity in regular society, however the recipients are limited by end stage kidney disease failure with requirements for high out of pocket expenditure on haemodialysis, clinic reviews and medication(47). This age stratification is comparable to other studies done in Africa where the median age for recipients is 37±3 years in Egypt and in South Africa(1,48) while in brazil the recipients are female predominantly and older at a mean age of 43.5 years(16) .

We found that the recipients had a median dialysis vintage of 18 months (11 to 30 months) prior to undergoing kidney transplant which is similar to the data from Kayima et al in 1996(3). This finding points to the fact that even with the increased provision of renal replacement therapy in the country and improved access to transplant programs patient haemodialysis vintage is unchanged and therefore there are other factors that would need to be explored in order to improve the uptake of transplant as a treatment modality. In our study the association between dialysis vintage and outcome of alive with functioning allograft or failed allograft and back to dialysis was 18 and 16 months was not significant (p-value 0.623 and 0.494 respectively. Patients also show a preference for long term haemodialysis as it is covered by the National Health Insurance Fund (NHIF) whereas post-transplant medication and care is not. Haler et al in a study done in Austria found a trend toward better allograft and patient survival with pre-emptive kidney transplant and dialysis vintage having a graded association but it was not a significant association (49).

Body mass index has been a factor in optimising the recipients and donors for potential transplant. Obesity with BMI more than 30Kg/m^2 is a recognised factor in the development of CKD post-transplant. In our population the mean BMI was 21.5 Kg/m2 which is within normal limits for a recipient this has been influenced by selection criteria of donor-recipient pairs for the transplant.

Blood group, Human Leucocyte Antigen match and Immunosuppressive medication

The local pre-transplant work-up protocol includes ABO blood group and HLA match as a requirement aimed at optimising and influences induction immunosuppressant medication and prevention of organ rejection. Blood group O was found to be predominant in both donors (69.6%) and recipients (60%) and this could be a reflection of the predominant blood group in our population. In our transplant work-up we continue to match our patients at 6 HLA antigens (i.e. HLA-A, B, DR, Loci). In this study most of the recipients were matched at above 3 of the 6 loci with those who are matched at less than 3 receiving added basiliximab (an Interleukin-2 receptor antagonist for activated T lymphocytes which is the pathway responsible for activating cell-mediated allograft rejection). In this study we found that there was not significant relationship between the HLA match and the outcome of alive with a functioning graft or alive with failed graft and back to dialysis or dead with or without functioning graft. Recipients who had induction with basiliximab also had long term allograft survival similar to those who did not receive it, this may suggest that there are other factors to consider for long term success or failure of the graft.

In addition to the standard use of methylprednisone on induction all recipients had triple therapy with a calcineurin inhibitor, mycophenolate analogue and steroid for maintenance immunosuppressant therapy. Notably tacrolimus was introduced later into the transplant program with the first recipient receiving a dose in the year 2013 2013, prior to this, cyclosporine was widely used. Azathioprine was not used in any of the recipients for induction immunosuppressant but a few cases were noted to have had these changes made to their regimen during follow-up. This trend is in keeping with other major centres around the world that uses tacrolimus in post-transplant follow-up(45,46). These immunosuppressive agents, as expected, had significant association with recipient survival with functional grafts. The continued use of these medications is essential for graft survival.

Morbidities post-transplant

Diabetes Mellitus and hypertension were the most prevalent primary diagnosis in ESKD at 28% and 84.6% respectively this is comparable to studies done previously in Kenya (3,5) and from others in Egypt (48), Cameroon (50) and Brazil (16). Diabetes Mellitus is an important cause of chronic kidney diseases and increases cardiovascular related mortality risk in this population. Hypertension has been documented as both a cause of CKD and a complication as well; it also increases the pill burden in both pre and post-transplant recipients. High pill burden which has been associated with decreased medication adherence as found by Bore et al in KNH (51). The clinically diagnosed chronic glomerulonephritis was noted to be in 47% of the recipients pre-transplant which is in keeping with studies done from Cameroon (50) and Australia (52). Post-transplant diabetes has been noted to have a prevalence of 2% to 53% in various studies (53) and in our study we found 12..8% of the recipients which is similar to findings from an earlier study done on dysglycemia in post kidney transplants at our institution by Tammy et al. (54) and similar to a study in India noting the prevalence at 17.2% in the 250 patients they assessed (55) which is within the global prevalence. The immunosuppressive agents, tacrolimus and prednisone, are used are known to be diabetogenic and contribute to the incidence of glucose metabolism disorders have been in use in our recipient population as well.

Graft dysfunction is a recognised concern as soon as kidney transplant becomes an option of treatment. The aetiology is multimodal and may include recurrence of primary disease, drug adverse effects, infection and de-novo disease. We found that a third of recipients (37.6%) had graft dysfunction. With biopsies done on grafts only when there is significant dysfunction the

causes of the dysfunction is usually not known. This shows that there should be a low threshold to performing transplant biopsies which may improve outcomes

Among the infections considered in this study cytomegalovirus (CMV) whether probable or confirmed was noted in 15 (12%) of recipients. This is in keeping with earlier results done in the kidney allograft recipients in 2016 in KNH by Barasa et al. (56). Tuberculosis (TB) is a leading infection following renal transplant with reactivation being the most common infection mode. The use of cyclosporine is usually associated with early onset of TB (57). In Asia the prevalence post-transplant is 3.1 to 15%, 1.5-3.5% in the Middle East and 1.5-8.5% in South Africa (58,59). In our study we noted TB in 8% of recipients the patient characteristics for these patients would need further review to ascertain the use of specific immunosuppressive agents or other factors that may have made them more susceptible. There were no documented cases of post-transplant lymphoproliferative malignancies in our study. This may not necessarily be a case of lowered index of suspicion as the risk is known to be lowest after kidney transplant (0.8%-2.5%) (60). On the other hand we found Kaposi sarcoma in 4 (3.2%) of the recipients and half of them had an eventual loss of graft although it was not significant to overall allograft survival

Recipient and Allograft status

The outcomes of patients weighs heavily on the minds of the transplant teams. We looked into the various possible outcomes at the end of the study. Recipients who were alive with a functional allograft were 60.8% while 39.2% had lost their allograft. Among those who had lost the allograft, 11.2% were alive, which included one person (0.8%) who had lost the initial allograft and had received a re-transplant. The others (28%) were deceased. They included 17.6% who had a functional allograft at the time of death. When looking at the overall allograft survival of the recipients we noted that at the end of one year was 91.4%, at five years was 64% and at ten years was 37.2%. In the study done by Kayima et al in 1996 a graft survival of 93% and 86.6% patient survival rate at one year was observed which is comparable to our study(3). Our allograft survival findings are lower than those from studies done in Egypt which is at 97% at one year, 86.6% at five years and 67.9% (61) at ten years and Brazil at 95.2% at one year, 88.9% at five years and 81.1% at ten years (62). The factors that lead to the reduction in allograft survival will need to be explored to improve future outcomes of allograft survival.

When looking into correlates that may have influenced the outcomes we did not find any significant relationship between recipient age (p-value 0.899), haemodialysis vintage (p-value 0.328), HLA match, or comorbidity (Diabetes pre-transplant (p-value 0.193), post-transplant (p-

value 0.251), on the allograft survival. There was a trend toward improved survival for the male recipients but it was not significant (p-value 0.093).

We do not routinely have prophylaxis for CMV in our transplant program. The cost benefit analysis shows that it increases the financial burden to recipients due to the cost, drug interactions and availability of medication but the benefit would be improved survival. In our study we noted that almost half of those who had probable or confirmed CMV had a loss of graft but was not significant. Similarly for TB with prophylaxis instituted in the program half of recipients with active disease lost their grafts but it was not significant. Kaposi Sarcoma was also noted to have a similar trend with half of the recipients having graft loss but it was not significant.

The use of basiliximab on induction was significant on allograft survival with a p-value of 0.037 as well as the use of tacrolimus (p-value 0.018) and cyclosporine (p-value 0.018). Although when tacrolimus was compared with cyclosporine for allograft survival, cyclosporine was not found to be inferior to tacrolimus on allograft survival. The data from the symphony trial (63) as well as other studies (64) are more favourable toward use of tacrolimus and this is also part of the KDIGO guideline(65) on use of tacrolimus as first-line immunosuppressive therapy post-transplant.

6 CONCLUSION

Donors and recipients are young (36years and 39years respectively) and predominantly male who are selected for normal BMI with donors being mostly first degree relatives. A median haemodialysis vintage pre-transplant has remained unchanged in our study from previous studies done in this population. Pre-transplant comorbidity included hypertension, diabetes and glomerulonephritis and post-transplant there was an incidence of post-transplant diabetes of 12.8% with hypertension remaining unchanged and allograft dysfunction accounting for of the post-transplant comorbidity. Infections including tuberculosis and cytomegalovirus and malignancy of Kaposi Sarcoma had a trend toward nearly 50% graft loss but this was not noted to be significant and this would need to be considered on informing choice of medications for prophylaxis on allograft survival. The allograft survival was noted to be 91.4% at one year, 64% at five years and 37.2% at ten years. HLA match, haemodialysis vintage, comorbidity pre and post-transplant did not significantly impact the allograft survival. Recipient sex had a trend toward male sex having better allograft survival but was not significant. Basiliximab was used for recipients who had lower than 50% HLA match and thus increased immunologic risk and this was found to have an improved survival to mirror the recipients who did not receive the drug as part of their induction thus justifying its continued use. Of note cyclosporine was not inferior to tacrolimus among our population on the allograft survival.

7 LIMITATIONS OF THE STUDY

1. This was a retrospective single centre study which had inherent issue of missing data as records are manually filed. We were able to pick all available files and review them which helped to counter this limitation.
2. There is an aspect of bias as files that were assessed were as per those that were retrieved from the available medical records.
3. Recipients who were not seen in the clinic for more than 2 years from the end of the study review month in November 2021 were assigned the worst possible outcome of being dead with a non-functional graft. Closer monitoring and follow-up of recipients to maintain contact and status is important for future studies and survival analysis.

8 RECOMMENDATION

1. The medical records department were commendable for being able to retrieve most of the files but it would be an improvement for us to recommend a digital registry of all donors and recipients would be of benefit to further study the patient characteristics and long term follow up to allow optimisation of care and improved outcomes of long term survival as well as capacity to retrieve data for future studies.
2. Follow up studies to include
    a. Longitudinal studies retrospective and prospective to document and follow up on outcome to elucidate causes of graft failure.
    b. A larger cohort including all centres within the region that are conducting kidney allograft transplant with the view to review all recipients with allograft loss for correlates
3. Support for the continued use of basiliximab in potential kidney transplant recipients with HLA mismatch.
4. The Kidney transplant program is a viable treatment modality with improving allograft survival and the modality should be encouraged and supported.

APPENDICES

APPENDIX 1: Study proforma

SECTION A: SOCIODEMOGRAPHIC

A1: Serial Number: ……..

A2. Recipient sex: …….. [1] Male [2] Female

A3. Donor sex: …… [1] Male [2] Female

A4. Donor age (year): ……..

A5. Donor to recipient relationship:……

A6. Date of transplantation: (DD/MMM/YYYY) ……

A7. Age at transplantation (year) ……..

B: CLINICAL DATA

B1. Duration on haemodialysis (months): ……

B2. Documented underlying morbidities

	B2.1Before transplant		**B2.2After transplant**	
B2.1.1 Diabetic: ……	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**
B2.1.2 Hypertensive ……	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**
B2.1.3 Glomerulonephritis ….	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**
B2.1.4 Obstructive uropathy …	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**
B2.1.5 Autoimmune disease ….	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**
B2.1.6 Others ……	**[1] Yes**	**[2] No**	**[1] Yes**	**[2] No**

B2.3 Height (cm) …… B2.4 Weight (kg): ……..

ABO blood group and HLA Match			
B2.5	Donor is …….. to the recipient	Donor	Recipient
B2.6	Donor age :----- years		
B2.7	Donor sex: [1] male [2] Female		
B2.8	Donor ABO blood group		
B2.9	HLA		
B2.10	A(1^{st} locus/2^{nd} locus)		
B2.11	B(1^{st} locus/2^{nd} locus)		
B2.12	DRB1(1^{st} locus/2^{nd} locus)		
	HLA-A,B and DRB1 match		

B2.13 Duration of transplant surgery [1]1-2H 59M [2] 3-5H 59M [3] More than 6H

B2.14 Returned to operation theatre within 24 hours post op……. [1] Yes [2] No

Induction medication

B3. Methyl predinisolone: ……. [1] Yes [2] No

B4. Basiliximab: ……. [1] Yes [2] No

B5: Tacrolimus ……. [1] Yes [2] No

B6: Cyclosporine: ……. [1] Yes [2] No

B7: Mycophenolic analogue [1] Yes [2] No

B8. Azathioprine ……. [1] Yes [2] No

B10: other classes of medication:……. [1] Yes [2] No

B11 Did the patient develop post-transplant conditions? …. [1] Yes [2] No

B11.1 Tuberculosis: ……[1] Yes [2] No

B11.2 Cytomegalovirus: ……. [1] Yes [2] No

B11.3 Graft dysfunction ……. [1] Yes [2] No

B11.4 Kaposi sarcoma ……. [1] Yes [2] No

B11.5 Post transplant lymphoproliferative malignancy: …. [1] Yes [2] No

B11.6 Others……. [1] Yes [2] No

C. OUTCOMES

		Immediately after Transplant	At Three Months	At six months	At 12 months
C1.1	Urea (mmol/l)				
C1.2	Creatinine (umol/l)				
C1.3	Potassium (mmol/l)				
C1.4	Sodium (mmol/l)				
C1.5	eGFR (ml/min/1.73m^2)				

C1. Last medical review date: (dd/mm/yyyy) ……

C2. Serum creatinine (umol/l) ……. C3 Urea (mmol/l): ……..

C4. eGFR (ml/min/1.73m^2): ……..

C5. The recipient is ……[1] Alive with functional allograft

[2] Alive with failed graft and return to dialysis

[3] Re-transplanted

[4] Dead with non-functioning graft

[5] Dead with functioning graft

[6] Status not known, lost to follow up

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