KIDNEY ALLOGRAFT FUNCTION AND ITS DETERMINANTS AT 12 MONTHS POST TRANSPLANTATION IN KENYA

PRINCIPAL INVESTIGATOR

DR. DAVID MARTIN ATUHE

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EAST AFRICA KIDNEY INSTITUTE

UNIVERSITY OF NAIROBI, KENYA

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Declaration:

This proposal is my original work being submitted as part fulfilment for the award of a Fellow of nephrology at the East Africa Kidney institute at the University of Nairobi, and that to the best of my knowledge has not been presented at any other University or Institution of higher learning

Signed: .....

Date: 8/9/21

PRINCIPAL INVESTIGATOR

DR. DAVID MARTIN ATUHE

MBCh.B, MMED (Internal Medicine)

NEPHROLOGY FELLOW OF THE EAST AFRICA KIDNEY INSTITUTE

Approval by supervisors

This proposal has been submitted with the approval of my supervisors

PROF. JOSHUA K. KAYIMA

Associate Professor of Internal Medicine, Consultant Physician & Nephrologist

University of Nairobi, School of Medicine

Department of Clinical Medicine and Therapeutics

Signature.....Date 09/9/2021

PROF. SETH O. McLIGEYO

Professor of Nephrology, Consultant Physician & Nephrologist

Department of Clinical Medicine and Therapeutics

University of Nairobi, School of Medicine

Signature .....Date 8/9/21

DR. JOHN NGIGI N.

Consultant Physician & Nephrologist

Head of Renal Department,

Kenyatta National Hospital

Signature .....Date 9.9.21

DR. AHMED P. SOKWALA

Assistant Professor of Internal Medicine, Consultant Physician & Nephrologist,

The Aga Khan Medical College, East Africa

Aga Khan University Hospital

Signature .....Date 14/9/2021

Dedication

To my parents whose life inspired me. To my wife and daughter whose sacrifice made this possible.

Acknowledgments

Almighty God

International Society of Nephrology, Uganda Cancer Institute, Uganda Ministry of Health and St. Francis Hospital, Nsambya

The Late Dr. A. J. O. Were (R.I.P) for inviting me to E.A.K.I

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Doctors and Nurses who took time to document findings

My family for the sacrifices made

Table of Contents

List of tables:

List of figures

List of abbreviations and acronyms

ABMR	Anti-body Mediated Rejection
AKUH	Aga Khan University Hospital
AKI	Acute Kidney Injury
AHA	American Heart Association
ACC	American College of Cardiology
ANZDATA	Australia and New Zealand Dialysis and Transplant registry
AOD	Adjusted Odds Ratio
BMI	Body Mass Index
CI	Confidence Interval
CIT	Cold Ischemic Time
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
DGF	Delayed Graft Function
eGFR	Estimated Glomerular Filtration Rate
ESKD	End Stage Kidney Disease
GFR	Glomerular Filtration Rate
HLA	Human Leucocyte Antigen
IQR	Inter Quartile Range
KNH	Kenyatta National Hospital
KTR	Kidney Transplant Recipient
LDT	Living Donor Transplant
LKD	Living Kidney Donor
MDRD	Modification of Diet in Renal Disease
MOST	Multinational Observational Study in renal Transplantation
QoL	Quality of Life
SD	Standard Deviation
TCMR	T-Cell Mediated Rejection
UK	United Kingdom
UNOS	United Network for Organ Sharing
WIT	Warm Ischemic Time

Operational definitions:

- Late graft function: Dysfunction that occurs 6 months after kidney transplantation[1].
- Graft dysfunction in this study: Serum creatinine ≥132.6 umol/l at 12 months[2].
- Hypertension: Office blood pressure ≥130/80 as per AHA/ACC 2017 guideline[3]

ABSTRACT

Background:

Kidney transplantation is a treatment of choice for most patients with End Stage Kidney disease. Kidney allograft function at one year provides prognostic information and is influenced by donor, recipient and other factors. These determinants have not been described in Kenya. This study aimed at assessing the kidney allograft function status at one-year post-transplant and describing risk factors of allograft dysfunction. This information shall help clinicians identify patients at risk of poor function and prioritize early interventions. This shall improve patient outcomes and ensure longevity of the transplant program.

Objective:

To assess kidney allograft function and its determinants in KTRs transplanted at Kenyatta National Hospital and Aga Khan University Teaching Hospital at 12 months post-transplant over 10 years.

Methods:

This was a retrospective cohort of all available charts at two transplant centers (Kenyatta National Hospital and Aga Khan University Hospital) of a period of ten years. Selected demographic, clinical and biochemical data of both the recipients and donors were extracted by using a questionnaire. Data entry was done using Kobo tool box and exported to R Software for analysis. Missing data was imputed by multiple imputation methods, Bivariate analysis was done to describe valuables associated with allograft dysfunction. Mixed effect logistic regression model was used to establish determinants of allograft dysfunction at one year. Level of significance was 0.05.

Results:

Two hundred and forty patients were transplanted over the 10-year period. Of these only 150 charts were available for analysis. The donor median age was 33 years (IQR (28, 39)) with 59% of them being male. Eighty five percent of donors were first degree relatives. Majority of recipients were male (71%) with a median age of 36 years. The prevalence of allograft dysfunction was 22.6%. Pre transplant blood transfusion was common (59%).

Patients with allograft dysfunction were more likely to be male (p value = 0.011) and married (p value = 0.032). We observed a higher rate of pre-transplant blood transfusion (p value = 0.016), receiving pulse therapy with methyl prednisone (p value <0.001) and were more likely to have been diagnosed with AKI in the first 2 months after transplantation (p value < 0.001). Also, had higher creatinine levels at discharge, one month, three months, 6 months and had a higher

calculated average of annual creatinine (all with p value < 0.001). A longer duration in surgery more than 3.5 hours was more prevalent in patients with allograft dysfunction (p value = 0.04). Acute Kidney Injury within the first year ((P value 0.008 Adjusted Odds Ratio (AOD) of 13.2 (95% CI 1.96-88.05)) and transplant surgery of more than 3.5 hours ((P value 0.018 AOD 5.06 (95% CI 1.32-19.34) were associated with kidney allograft dysfunction at 12 months.

Conclusion:

1 in every 5 kidney transplant recipients had allograft dysfunction at 12 months, this was associated with development of acute kidney injury post-transplant and transplant surgery of more than 3.5 hours.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background information

Kidney transplantation remains the preferred choice for treatment for most patients with end-stage kidney disease (ESKD) [4]. Kidney transplant recipients (KTRs) benefit from a higher quality of life (QoL)[5] and have a better outcome in terms of survival than their counterparts receiving maintenance dialysis or those on the transplant waiting list[6]. In living donor transplant programs, a prospective patient with ESKD is matched with a healthy suitable donor[7]. A selected donor kidney is extracted through an incision on the donor's abdomen through a process known as nephrectomy. The extracted donor kidney is then placed in the lower abdomen of the ESKD patient in the same sitting. The donor kidney now attached to the recipient, is called a kidney allograft.

Allograft survival is the time between transplantation and allograft failure as indicated by the need to return to maintenance dialysis or re-transplantation. Over the last decade, this has improved especially in the first year, however, the improvement in allograft survival has not been seen in the longer-term survival after one year[8]. Advances in immunosuppressive drugs utilized during both maintenance and induction phase, and those used to treat acute rejection have greatly improved allograft survival [9].

Factors affecting outcome of living donor transplantation are; donor variables that include a pre-donation estimated Glomerular Filtration Rate (eGFR) of <80ml/min[10], age greater than 45 years[11,12], and donor-recipient size mismatch[13]. Recipient variables include obesity [14,15], presence of co-morbidities like diabetes mellitus[16], peripheral arterial disease[17], Systemic Lupus Erythematosus and anti-phospholipid syndrome[18,19], hepatitis C and HIV disease [20,21], and recurrence of primary glomerulonephritis. Other variables include immunosuppression used[22], surgical protocols [23], prolonged warm and cold ischemic times (WIT and CIT respectively), Human Leukocyte Antigen (HLA) matching between donor and recipient [24,25] and presence of donor specific antibodies after transplant[26].

Graft function is usually estimated by using serum creatinine [27]. Other methods used include

urinary protein excretion and urinary volume in the very early peri-transplant period[28].

Renal function during the first year after transplantation has been found to be an important parameter impacting long-term graft survival [29]. The serum creatinine level at twelve months after transplantation is a risk factor for future outcomes. Recipients who have a serum creatinine level of ≥1.5 mg/dl (132.6 µmol/l) and exhibit an increase in creatinine of ≥0.3 mg/dl (26.5 µmol/l) between 6- and 12-months post-transplant have a significantly lower expected graft half-life than others without. This means we can therefore use the serum creatinine level at 12 months and the change in serum creatinine between 6- and 12-months as surrogate markers for renal function and predictors of long-term renal allograft survival[30].

This study thus aims to describe the kidney allograft function of KTRs at one year and assess the associated determinants at two transplant centers in Kenya over a 10-year period.

1.2 Problem statement:

Kidney allograft dysfunction is associated with patient and care giver psychological stress[31]. It is also associated with significant morbidity and an increased all-cause mortality[32]. Furthermore, it predisposes to allograft loss with subsequent re-initiation of dialysis and/or re-transplantation which is further distressing to patient[33]. Re-transplantation also brings with it economic, technical and immunological challenges[34].

The burden of late graft dysfunction at 12 months post-transplant and its associated factors have to our knowledge not been described in Kenya.

1.3 Aim of the study:

This study aimed at describing the kidney allograft function of KTRs at one year and assessing the associated determinants at two transplant centers in Kenya over a 10-year period.

1.4 Research question

In kidney transplant recipients at Kenyatta National Hospital and Aga Khan University Hospital over a period of ten years, what is the prevalence of kidney allograft dysfunction and what are its determinants at 12 months post kidney transplant.

1.5 Justification

This study has documented the kidney allograft function status at one year in KTRs within our population. We now know that more than 70% of allografts are functioning well by one year.
The study has shown the burden of late graft dysfunction at 12 months post kidney transplant. Being the first study of its kind, we hope this will increase awareness of this particular problem. A serum creatinine of 132.6 µmol/l and above shall be used as a marker of allograft dysfunction at one year[2] and this shall help with prioritization and timing of follow up consultations for the affected patients.

Furthermore, the study has described demographic, clinical and biochemical characteristics of patients diagnosed with late graft dysfunction. Such phenotypes like male gender, high discharge creatinine values, long surgery duration are easy to identify and isolate for close monitoring. Whereas empiric pulse therapy with methyl prednisone is unavoidable in circumstances of clinical rejection, this study has provided more basis for the need to always clarify the type of rejection for optimization of therapy. Acute Kidney Injury is independently associated with allograft dysfunction, this information shall be used to put up strict AKI diagnosis and follow up protocols within the transplant program to achieve timely aversion of the process and potentially improve outcome.

1.6 Objectives of the study

1.6.1 General objective

To assess kidney allograft function and its determinants in KTRs transplanted at Kenyatta National Hospital and Aga Khan University Teaching Hospital at 12 months post-transplant over 10 years.

1.6.2 Specific objectives:

i. To describe selected pre-transplant donor and recipient characteristics including age, gender, BMI, pre-donation kidney function by DTPA, HLA match, dialysis vintage and proteinuria.
ii. To describe the frequency of kidney allograft recipients' primary diagnoses
iii. To describe individual kidney allograft recipient's serial serum creatinine level
iv. To describe frequency of selected peri and post-transplant practices and complications

including blood transfusion, duration of surgery, length of stay in hospital, empiric methyl prednisone therapy use, Acute Kidney Injury and infection diagnosed.

v. To determine serial graft function using eGFR calculated by MDRD formula at 1^{st}, 3^{rd}, 6^{th}, and 12^{th} month post kidney transplant

vi. To determine the prevalence of kidney allograft dysfunction at 12 months post kidney transplantation

1.6.3 Secondary objective

i. To compare demographic, clinical and biochemical factors in KTRs with normal kidney allograft function and kidney allograft dysfunction transplanted at Kenyatta National Hospital and Aga Khan University Teaching Hospital at 12 months post-transplant.

CHAPTER TWO

2.1 Literature review

2.1.1 Introduction to kidney transplantation

Kidney transplantation remains the preferred choice for treatment for most patients with end-stage kidney disease (ESKD)[4]. Kidney transplant recipients (KTRs) benefit from a higher quality of life (QoL)[5] and have a better outcome in terms of survival than their counterparts receiving maintenance dialysis or those on the transplant waiting list[6]. In living donor transplant programs, a prospective patient with ESKD is matched with a healthy suitable donor[7]. One of the donor kidneys is removed through an incision on the donor's abdomen also called nephrectomy. This donor kidney is then placed in the abdomen of the ESKD patient in the same sitting. The donor kidney now in the abdomen of the recipient, is called an allograft kidney.

Allograft survival is the time between transplantation and allograft failure as indicated by the need to return to maintenance dialysis or re-transplantation. Over the last decade, this has improved especially in the first year, however, the improvement in allograft survival has not been seen in the longer-term survival after one year[8]. Considerable percentage of the achievement of improved allograft survival is attributed to advances immunosuppressive drugs utilized during both maintenance and induction phase, and those used to treat acute rejection[9].

2.1.2 Kidney transplant in Kenya

The first kidney transplant in Kenya was in the year 1978[35] after which followed a lot of advocacy for the practice to be made widely available for patients with ESKD. By 1990, KNH had already recorded 15 living donor KTRs. That time, allograft survival rate at one year was recorded at 93%[36]. As per 2019, Kenya has a total of 9 hospitals offering renal transplant services, and a total of 517 KTRs recorded by time of accessing report[37]. A study at KNH in 2014 in 94 KTRs reported renal allograft survival as 88.7%, 88.7%, 88.7% and 82.6 % at one, two, three and 4-year post renal transplant[18]. All of the transplant programs are living donor programs and a national kidney transplant guideline is yet to be launched.

2.1.3 Assessment of graft function

Urine volume, urine protein excretion and creatinine all have been evaluated as measures of graft function.

In the peri-transplant phase, urine volume has a huge role in assessing allograft function and especially predicting dysfunction [38] . Polyuria, however may occasionally be a manifestation of saline or water diuresis due to tubular damage[7]. Passing of adequate urine usually results in decreased serum creatinine and blood urea nitrogen, suggesting an improvement in overall kidney function of the patient.

Urine protein can be a marker of chronic kidney disease and may suggest graft dysfunction. However, it should be noted that some proteinuria after kidney transplant is due to native kidneys and not the graft kidney[39].

Serum creatinine concentration evaluation is an easy, inexpensive and widely available tool for estimating GFR and it is fairly effective for detecting acute changes in allograft function. Unfortunately, no eGFR estimation formula has shown consistent superiority over other formulas despite several studies. In fact, a systematic review of 23 studies on adult KTRs who had been transplanted more than 6 months prior compared creatinine-based GFR estimation equations against GFR determination using plasma or renal clearance of inulin, radioisotopes, or non- radiographic contrast and revealed very biased results and blamed the heterogenicity of the individual studies[40]. Two MDRD formula exist, the 6 variable and 4 variable formulae[41,42]. However, monitoring of allograft eGFR calculated using MDRD results in more consistent results than using CKD-EPI equation[43].

2.1.4 Significance of 1-year post kidney transplant creatinine

The degree of GFR impairment at 1-year post kidney transplant has a prognostic value and corresponds with a lower GFR at five years, raises the probability of eventual allograft failure, and cardiovascular death. In fact, GFR at 12 months post kidney transplant is increasingly being used as a surrogate endpoint for long-term allograft outcome in clinical trials[44,45].

In a study that aimed at examining renal function in the first year of kidney transplantation as an independent variable in determining long-term renal graft survival, more than one hundred

thousand adult KTRs (including 28,160 living donor transplants) in the United States were studied. The study noted that increases in both the level of serum creatinine value at 12 months and in the change in creatinine level between six and 12 months resulted in increasing risks of allograft failure and thus concluded that these two variables correlated best with long-term renal graft survival[29].

Another retrospective review was conducted on clinical data from 433 adult cadaveric donor kidney transplantations to assess risk factors for lower eGFR at 3- and 12-months post transplantation and examine the effect of first year allograft function on graft and patient survival. Similarly, lower eGFRs at 3 and 12 months were found to be linked to worse allograft survival[2].

Similar conclusions were drawn when 10,692 KTRs on cyclosporine were assessed in the Neoral-MOST (Multinational Observational Study in renal Transplantation). Graft function at 12 months was affected by similar factors that influence allograft survival such as delayed graft function and acute rejections and was predictive of allograft function at 5 years post kidney transplantation[46].

2.1.5 Factors that affect graft survival

2.1.5.1 Donor factors

Data from New Zealand and Australia transplant and dialysis (ANZDATA) Registry that included 5684 participants revealed a statistically significant association of obesity to delayed graft function (DGF) and also 6-month acute rejection risk[15].

Pre-donation eGFR below 80ml/min in a living donor program resulted in a statistically significant relative risk for graft loss of 2.28 in a study involving 344 living donated kidney transplantations in Sweden[10].

A retrospective study done at the Cleveland clinic to assess factors in the donor community that affect live donor allograft outcomes compared outcomes of recipients of donors who were either less or more than 45 years of age, and indeed, receipt of a graft from the older group was independently correlated with poorer allograft function at two years post kidney transplantation[12]. Furthermore, when the UK transplant registry data were scrutinized to determine outcomes of about 3000 kidney transplants from living donors, inferior graft survival

(as defined by time to allograft nephrectomy, re-initiation of dialysis or death – which ever came earlier) was found to be associated with donors who were 60 years and older[11].

Donor-recipient size mismatch is also of concern especially if the donor is older. Size mismatched offer better graft survival if the donor is young[13].

2.5.1.2 Recipient factors

Recipient obesity defined as BMI ≥40kg/m^2 has been shown to be associated with an inferior transplant outcome. This study showed that patients in this category derive less benefit from transplantation compared to all other lesser BMI groups[14].

Other factors that affect graft outcome include co-morbidities including diabetes mellitus[47], peripheral arterial disease[17], prothrombotic states like Systemic Lupus Erythematosus (SLE) and Anti Phospholipid Syndrome (APS)[18,19] and Hepatitis C virus infection[20,21]. As an example, KTRs have poorer graft survival than their non-diabetic counterparts as shown by Wai H. Lim et al in the population cohort study that explored the ANZDATA registry. In this study, diabetic recipients had higher mortality rates (25.3 per 100) compared to the non-diabetic counterparts (11.5 per 100)[16].

Recurrence of primary disease has been known to occur with different diseases exhibiting different recurrence patterns and frequencies[47]. Ten percent of just above 700 first kidney transplant recipients proven by biopsy to have primary FSGS experienced disease recurrence in an ANZDATA registry analysis. Recurrence of disease was associated with inferior 5-year allograft survival rate of 52%[48].

2.1.5.3 Surgical factors

Apart from surgical skill of the surgeon, and the time taken during nephrectomy and re-implantation, the other factors that affect graft function and survival include Cold Ischemic and Warm Ischemic Times (CIT and WIT respectively)[49,50]. Prolonged CIT, the period during which the kidney is cold stored prior to implantation, has been shown over time to be associated with worse graft outcome in cadaveric kidney transplants, exhibiting higher rates of delayed graft function (DGF), acute rejection and worse long-term outcome[51]. In living donor transplant, these times can last less than an hour.

A study was done to determine the influence of CIT on living donor kidney transplant recipients[52]. Participants were separated into three clusters depending on CIT (less than 2 h, 2–4 h, 4–8 h). And indeed, after confounding factors were adjusted for, a relationship was noticed between CIT and level of serum creatinine at 12 months. In the same study, allograft failure risk was substantially higher in the 4-8-hour cluster relative to the ones with a CIT of less than 2 hours.

Warm ischemic time is also linked to graft failure as well as negative patient outcomes[53].

2.1.5.4 HLA compatibility

Tissue typing of recipients and donors determines their HLA match. HLA antigens are coded for on chromosome six, with half (one haplotype) inherited from each parent. The major histocompatibility class I HLA-A and HLA-B and class II HLA-DR antigens are routinely examined and confirmed, because allograft rejection responses are thought to frequently stem from mismatches at these alleles. Sensitization to HLA antigens usually happens when one is exposed to pregnancy, blood transfusion, or past transplantation. The presence of antibodies to donor- specific HLA antigens in the recipient may lead to hyperacute rejection[24]. Also, presence of donor specific antibodies (DSA) is a robust predictor of Antibody Mediated Rejection (ABMR) and thus has an undesirable impact on allograft survival[54].

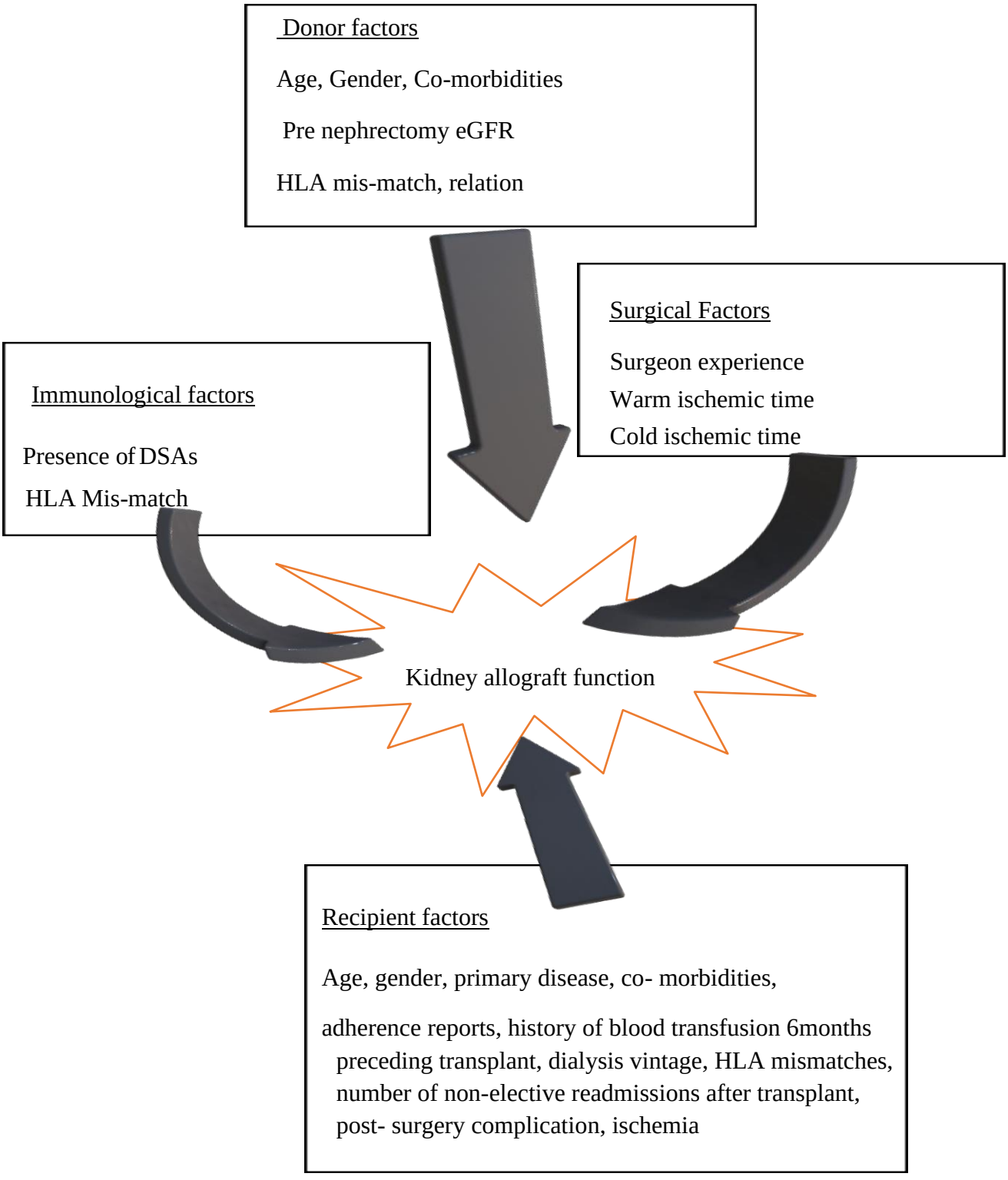

Figure 2.1: Conceptual framework

CHAPTER THREE

3.1 Methodology

3.1.1 Study design

This was a retrospective chart review of KTRs transplanted at Kenyatta National Hospital and Agha Khan University Teaching Hospital spanning over 10 years.

3.1.2 Study sites

Two study sites were chosen using a convenient sampling method because they were easily accessible but also to minimize travel, exposure to COVID-19 and costs during the pandemic

The study was carried out at Kenyatta National Hospital (KNH) and Aga Khan University Hospital (AKUH). Two sites were chosen to counter the inherent limitations of a retrospective study for example missing results that could potentially reduce the numbers of available charts. Two sites offered us a larger chart catchment area. KNH is a tertiary referral hospital located in the capital city of Kenya, Nairobi. KNH was established in 1900 and is the biggest hospital in the Eastern and Central Africa. It boasts of approx. 2000 beds and serves as the teaching hospital for the University of Nairobi, College of Health Sciences, both for the undergraduate and the post graduate programs. KNH transplant program is currently a living donor transplant program with 175 kidney transplants over the 10-year period[37].

The Aga Khan University Hospital in Nairobi is part of the Aga Khan Health Services. AKUH is a private, not-for-profit establishment. The hospital is a 254-bed long-term care institution offering general medical amenities, specialist services and diagnostic facilities and was established in 1958. It serves as the teaching hospital for Aga Khan University's Medical College with post graduate medical programs. As with KNH, the transplant program here is also living donor based, with 80 kidney transplants over the same 10-year period.

3.1.3 Study population

All patients transplanted at Kenyatta National Hospital and Aga Khan University Hospitals between January 2009 to December 2018. Records up to 2018 December allowed a one-year follow up to December 2019 of the charts.

3.1.4 Sampling

All available charts were reviewed and we conducted a post hoc power analysis to determine the statistical power of this study. For medium effect-size (h = 0.35) and a sample size of 150, the post-hoc analysis indicated that the study had a power of 85.8%. The method used for post-hoc analysis was the **arcsine transformation** which is the difference of proportion power calculation for binomial distribution. Furthermore, we ensured that 10 cases (charts) were used per variable to obtain results that are accurate and clinically useful [55].

3.1.5 Inclusion criteria

All charts of patients transplanted at Kenyatta National Hospital and Aga Khan University Hospitals between January 2009 to December 2018 with a documented serum creatinine measured at 6 and 12 months.

3.1.6 Exclusion criteria

i. Patients transplanted from other centers but on follow up from KNH or AKUH.

ii. Death before 12 months after transplant elapse

iii. Patients that experienced primary graft failure

iv. Patients that underwent a graft nephrectomy

v. Graft loss before one year

vi. Charts that missed outcome information i.e., serial 1-, 3-, 6- and 12-months creatinine measurements

3.1.7 Procedures

Medical records for the kidney transplant recipients were retrieved from health records and information office by principal investigator. These records were checked and data were extracted onto a data capture sheet (appendix 1).

3.1.8 Definition of variables

3.1.8.1 Dependent variable

Kidney allograft dysfunction was defined as creatinine ≥1.5mg/dl (132.6 mmo/l) at 12 months post- transplant.

3.1.8.2 Independent variables

3.1.8.2.1 Donor data

The donor variables include; age, gender, presence of pre-existing disease, smoking history, calculated Body Mass Index (BMI), HLA A, B and DRB1 mismatches, and pre-transplant donor eGFR as estimated by ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid) renal dynamic imaging.

3.1.8.2.2 Recipient data

The recipient variables include; age, gender, primary disease, co-morbidities, presence of proteinuria on dipstick, induction therapy, HLA mis matches, post-surgery complications (Clavien-Dindo classification as per appendix II)[23], creatinine level at discharge, creatinine level at 1, 3, 6, 9 and 12 months post kidney transplant, eGFR calculation using the 4 variable MDRD formula [41] .

I. History of peri transplant blood transfusion was defined as red blood cell transfusion with usage of a leucocyte filter within one week prior to transplant and up to discharge from hospital

II. Pre transplant blood transfusion was defined as history of red blood cell transfusion anytime during illness preceding the transplant, including immediate pre-transplant period as long as a leucocyte filter was not used

III. Dialysis vintage is the duration of time in months from initiation of dialysis to transplantation

IV. Recipient BMI was calculated and categorized as per WHO guidelines

V. Duration of surgery was defined in hours as the time from initiation of anesthesia induction to extubating the patient. Categories of ≤3.5 hours and >3.5 hours were deduced from the median duration of surgery for all participants.

VI. Length of hospital stay was defined in days as time from the day of transplant to discharge

VII. Documentation of sepsis was defined as any of documented fever above 37.2^{o}C or positive blood culture or documentation of diagnosis of sepsis or deviation from institutional antibiotic protocol.

VIII. Hypotension within transplant admission was defined as a systolic blood pressure below 90mmhg that occurred during and/or after surgery up to the day of being discharged from hospital.

IX. History of receiving methyl prednisone therapy was defined as empiric pulse therapy administered when rejection was suspected clinically or diagnosed, this therefore, did not include the pulse therapy administered at induction.

X. Any documented AKI in first year was defined as a serum creatinine ≥1.5 times more than the previous documented serum creatinine during a clinic visit.

3.1.8.2.3 Drugs used

These were classified into induction agents (basiliximab, methylprednisone, ATG) and maintenance immunosuppression drugs used.

3.1.8.2.4 Surgical variables

We considered ischemia time (both warm and cold) and surgery complications were classified according to Clavien-Dindo classification (appendix II).

3.1.9 Data management and analysis

3.1.9.1 Data collection and storage

Demographic, clinical, laboratory, treatment, and outcome data of the recipient and donors were extracted from the medical records using a data collection form (see appendix). Completion of the questionnaire/study proformas was verified by the investigator. The questionnaires were identified by unique codes that de-identified the data. The filled forms were kept under key and lock by the investigator and were re-checked for consistency and completeness before data-entry. The principal investigator followed up the discrepancies and incompleteness. Data-entry was done using Kobo Toolbox. Kobo Toolbox is a secure software for data collection. The data was protected using a username and password only known to the principal investigator.

3.1.9.2 Data analysis

i) Data Cleaning

The dataset was then exported from Kobo Toolbox to Microsoft Excel spreadsheets before importing them to R-software for cleaning and analysis. The continuous data was tested for presence outliers and the categorical variables for consistency in coding or levels. Missing values were indicated with NA for efficient data management. At the bivariate and multivariate

stage, the missing data was handled by using a statistically proven missing data technique called Multivariate Imputation by Chained Equation (MICE) [56].

ii) Descriptive statistics

Continuous variables were tested for normality using both histograms for visualization of the distribution and Shapiro-Wilk test for confirmation. There were no normally distributed variables hence we summarized by using frequencies and percentages and visualized using bar-charts, frequency tables or pie charts. The percentages were calculated according to the number of patients for whom data is available.

The prevalence of allograft dysfunction at 12 months was calculated as a proportion of patients with Serum creatinine ≥132.6 µmol out of the total sample size.

iii) Inferential statistics

A binary logistic regression model was used to model the determinants of kidney allograft function at 12 months (one-year). Multiple imputation was used to cater for missing data using several assumptions based on literature. We chose binary logistic regression because the response variable is binary, that is, normal kidney allograft function or kidney allograft dysfunction. During the regression modelling, the variable selection was made using backward selection, and results were interpreted using adjusted and unadjusted odds ratios and p-values. The level of significance was placed at 0.05, and significant results were those with p-values < 0.05. Besides, the regression was done at both univariate and multivariate levels so that the study can determine the effect of each covariate on the outcome individually and in the presence of other covariates. The covariates were tested for multicollinearity and only one of the correlated variables was kept for modelling in case of evidence collinearity.

3.1.9.3 Data presentation

Results were presented in frequency tables, bar charts and pie charts. Comparison tables were used to present data of the participants with and without late graft dysfunction with P-values obtained after correlating each variable with the outcome.

3.2 Ethical considerations

3.2.1 Approval and clearance

The study was approved by both the University of Nairobi/Kenyatta National Hospital Scientific and Ethics Committee and the Aga Khan University - Kenya Institutional Ethics Review Committee (IERC). A NACOSTI license was also acquired before the study began. After Ethics Committee approval, we obtained authority to utilize the medical records section in Kenyatta National Hospital and Aga Khan University Hospital from the health information and medical records departments in both hospitals.

3.2.2 Privacy and confidentiality

Coding of patients' information was done to protect privacy. The data extracted from charts did not include personal identifiers such as names, addresses, *huduma* numbers and dates of birth. The data was only identifiable by serial number. Information gathered was held in confidence by the investigators, and was only used for the study, not for any other purpose.

Chapter 4: Results

4.1 Chart Profile

A total of 240 patients were transplanted from KHN and AKUH over the ten-year period. One hundred and fifty charts satisfied eligibility criteria as shown in Fig 4.2.

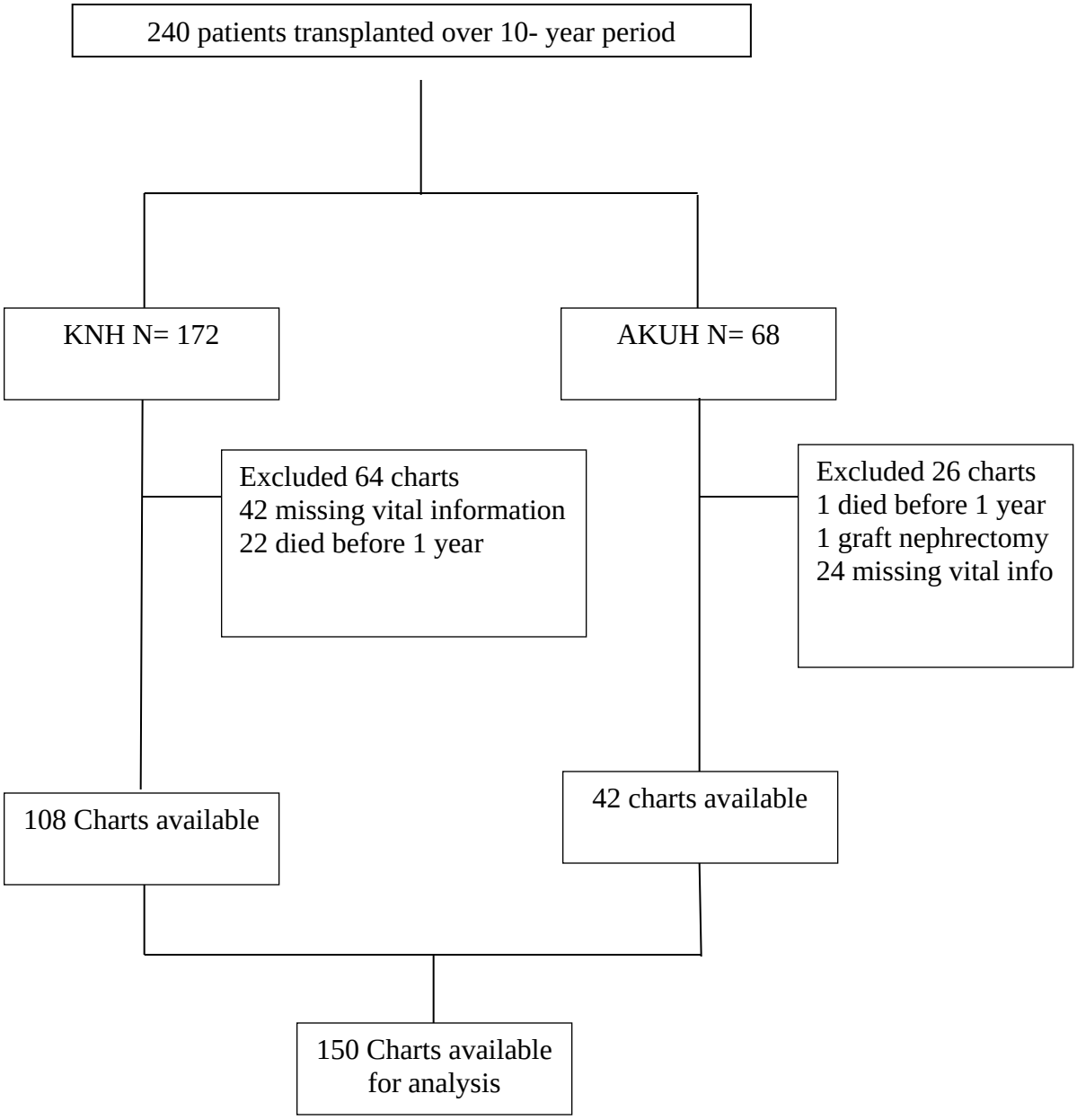

Figure 4.2: Chart profile

4.2 Baseline characteristics of study patients

4.2.1. Donor characteristics

Donor median age was 33 years (IQR (28, 39)) with 59% of them being male and 59% of all donors being married. Most donors 85% were first degree relatives, non-smokers (99%) and had no pre-existing illnesses (98%). The median donor BMI and total eGFR in this study was 24.7 kg/m^2 (IQR (21, 27.1kg/m^2)) and 95.5 ml/min/1.73m^2 (IQR (91.2, 99.9)) respectively. Majority (84%) of donor nephrectomies done were left nephrectomies. See table 4.1.

Table 4.1: Donor Baseline Characteristics

Characteristic	N (%), Median (IQR)
Donor Age	33 (28, 39)
Donor Gender	
Female	44 (41%)
Male	63 (59%)
Donor Marital Status	
Married	43 (59%)
Single	30 (41%)
Relation to Recipient	
1st degree	99 (85%)
2nd degree	17 (15%)
Donor Calculated BMI (Kg/m^2)	24.7 (21.0, 27.1)
Donor pre-nephrectomy Total eGFR	96 (91, 100)
Donor Kidney Side	
Left	58 (84%)
Right	11 (16%)

4.2.2 Recipient characteristics

4.2.2.1 Demographic characteristics

The median age of transplant recipients was 36 years (IQR (30,49 years)) and majority (71%) were male and married (66%). See table 4.2.

Table 4.2: Recipient Demographic Characteristics

Characteristic	N (%), Median (IQR)
Recipient Age	36 (30, 49)
Recipient Gender	
Female	44 (29%)
Male	106 (71%)
Recipient Marital Status	
Married	61 (66%)
Single	31 (34%)

4.2.2.2 Clinical characteristics

The most frequent primary diagnosis amongst the population studied was hypertension followed by diabetes mellitus (see Fig 4.3).

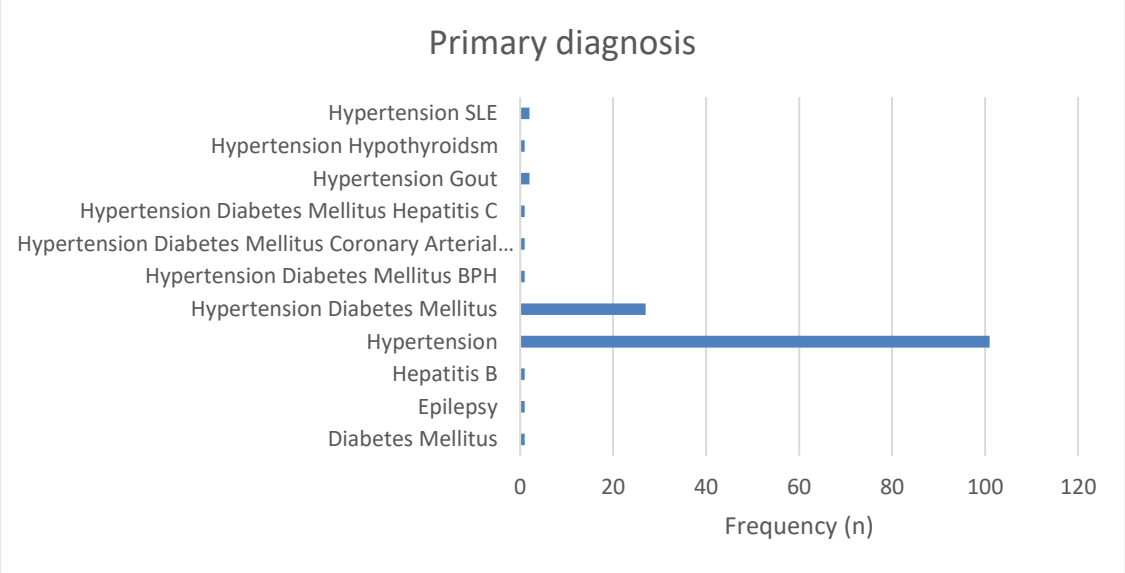

Figure 4.3 Primary diagnosis

Table 4.3 shows the selected clinical characteristics in the recipients. The median dialysis vintage was 14 months (IQR (8,21)). Most recipients were nonsmokers (93%). One in every 2 recipients (56%) had a normal BMI. Only 3.6% of recipients were obese. Fifty nine percent of recipients had received blood transfusion before transplantation and 57% underwent blood transfusion in and/or around the period of transplantation. Most (93%) of the transplant recipients had proteinuria on dipstick. Seventy three percent of recipients had a total HLA match

of 3 and above. Only 36% of recipients in this study received Basiliximab at induction. The transplant operation lasted a median of 3 hours (IQR (3,4)) and majority (60%) were classified as Clavien Dindo I. Only 18% of the transplant admissions were complicated with sepsis and recipients stayed a median of 9 days ((IQR (9,12)) after the operation. The median serum creatinine at discharge was 121 µmol/l (IQR 98, 146)). Forty-one percent of recipients had a documented episode of an infection during the first year after transplantation and majority of these were urological system infections (See Fig 4.4). Only one patient (0.9%) received prophylaxis against CMV. Acute Kidney Injury was diagnosed in 55% of recipients during the first year after transplantation and 32% of all recipients had a documented pulse therapy of methylprednisolone administered excluding the protocol induction therapy.

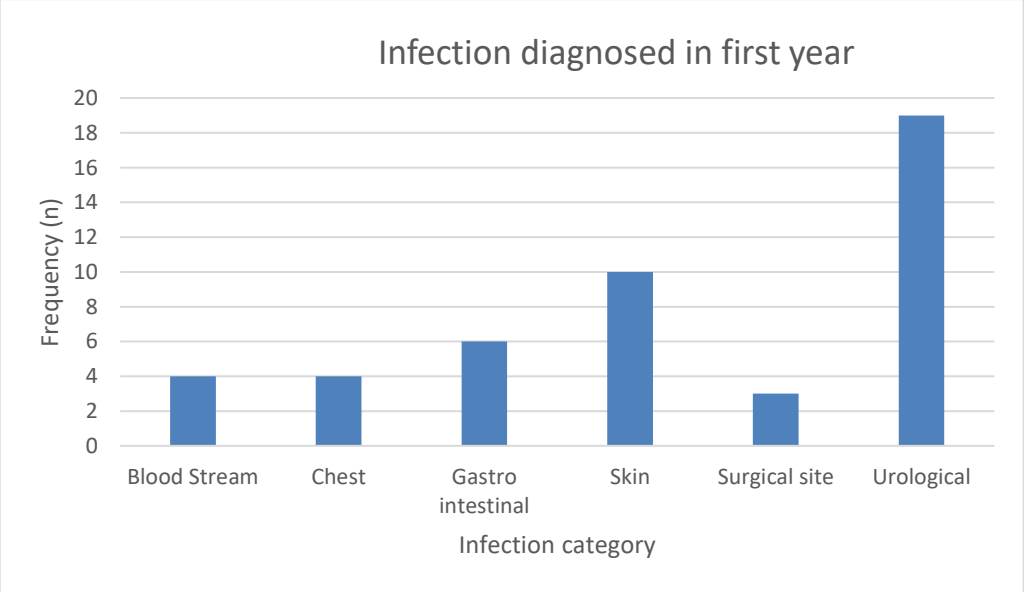

Figure 4.4 Infection diagnosed in first year

Table 4.3: Baseline Clinical Characteristics of recipients

Characteristic	**N (%), Median (IQR)**
Dialysis Vintage (months)	14 (8, 21)
Recipient History of Smoking	8 (6.9%)
Recipient BMI (kg/m^2)	
Underweight	20 (18%)
Normal	62 (56%)
Overweight	25 (23%)
Obese	4 (3.6%)
History of Pre-transplant Blood Transfusion	68 (59%)
Recipient History of Peri-transplant Blood Transfusion	69 (57%)
Recipient Urine Protein	93 (85%)
Total HLA Mismatch	
0-2	36 (27%)
3-6	95 (73%)
Basiliximab at induction	49 (36%)
Duration of surgery (hours)	3 (3,4)
Documentation of Sepsis during transplant admission	25 (18%)
Documentation of Hypotension During Transplant Admission	11 (8%)
Length of Hospital Stay (days)	9.0 (8.0, 12.0)
History of Receiving Methyl Prednisolone Pulse Therapy	37 (32%)
Any Documented Acute Kidney Injury AKI in First Year	62 (55%)
Specific Infection Diagnosed in First Year	46 (41%)
Creatinine Level at Discharge (µmol/l)	121 (98,146)

4.3 Trend of post-transplant eGFR

Figure 4.5 shows how eGFR was on a general upward trend amongst our KTRs in the study achieving a peak at the third month. At all the timelines, most of the KTRs were graded CKD G2. This data is represented in figure 4.6. Indeed by 12 months 77.4% of our KTRs are in Grade 1 and 2.

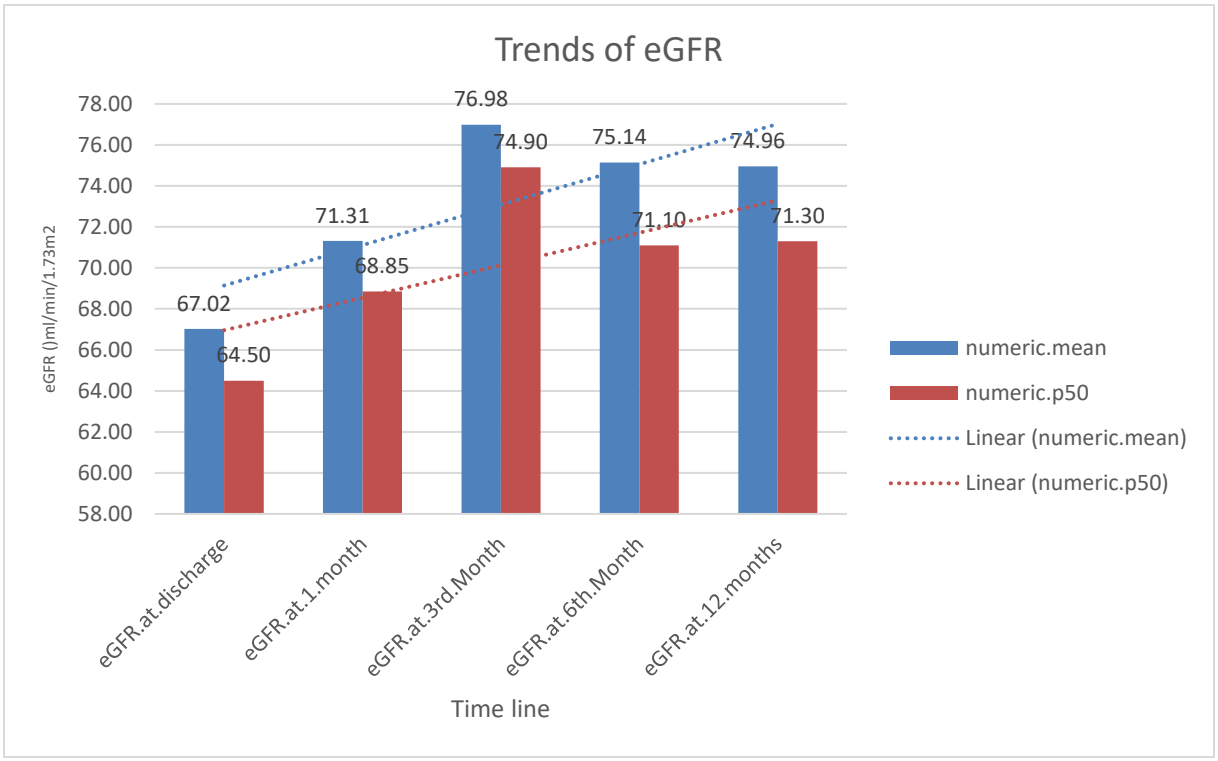

Figure 4.5 Trends of eGFR over one year post transplant

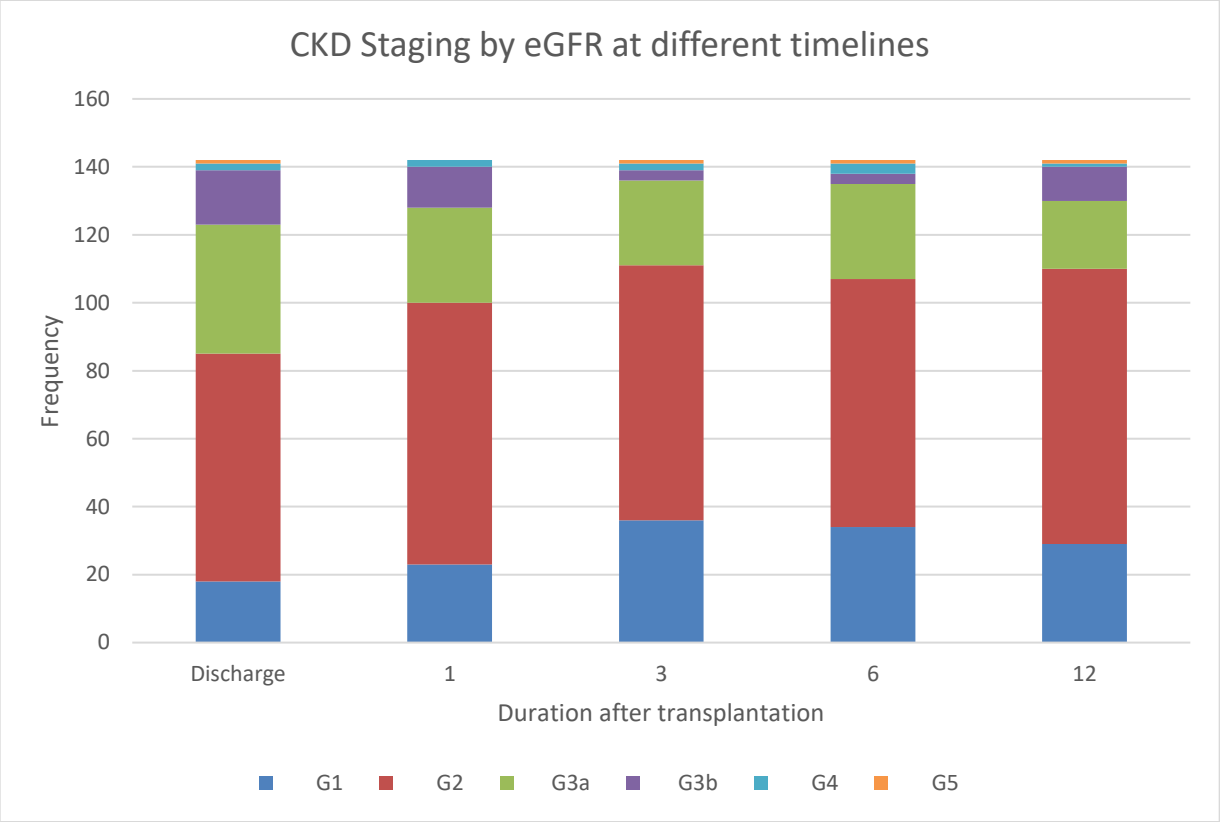

Figure 4.6 CKD grading

4.4 Prevalence of graft dysfunction:

The proportion of participants with graft dysfunction as defined by 12-month serum creatinine of ≥132.6µmol/l was 22.6%.

4.5 Clinical presentation of KTRs with allograft dysfunction

Patients with allograft dysfunction were more likely to be male (p value = 0.011) and married (p value = 0.032). KTRs had a higher rate of pre-transplant blood transfusion (p value = 0.016), receiving pulse therapy with methyl prednisone (p value <0.001) and were more likely to have been diagnosed with AKI in the first 2 months after transplantation (p value < 0.001). A KTR with graft dysfunction at 12 months was more likely to have higher creatinine levels at discharge, one month, three months, 6 months and had a higher calculated average of annual creatinine (all with p value < 0.001). A longer duration in surgery more than 3.5 hours was more prevalent in patients with allograft dysfunction (p value = 0.04). There was no difference between the two hospitals studied. This data is summarized in table 4.4 below.

Table 4.4: Clinical Presentation of KTR with Allograft dysfunction

Characteristic	Serum Creatinine at 12 months		p-value[2]
	<132.6 µmol/ = 116[1]	≥132.6 µmol/, N = 34[1]	
Recipient Gender			**0.011**
Female	40 (34%)	4 (12%)	
Male	76 (66%)	30 (88%)	
Recipient Marital Status			**0.032**
Married	43 (61%)	18 (86%)	
Single	28 (39%)	3 (14%)	
Recipient History of Pretransplant Blood Transfusion			**0.016**
No	42 (47%)	5 (20%)	
Yes	48 (53%)	20 (80%)	
History of Receiving Methyl Prednisolone Pulse Therapy			**<0.001**
No	68 (78%)	10 (36%)	
Yes	19 (22%)	18 (64%)	
Any Documented Acute Kidney Injury AKI in First Year			**<0.001**
No	50 (58%)	1 (3.7%)	
Yes	36 (42%)	26 (96%)	
Creatinine Level at Discharge >132.6µmol/l			**<0.001**
No	82 (72%)	11 (32%)	
Yes	32 (28%)	23 (68%)	
Creatinine Level at One Month	106 (91, 125)	134 (117, 172)	**<0.001**
Creatinine Level at Third Month	100 (86, 116)	130 (110, 156)	**<0.001**
Creatinine Level at 6th Month	98 (86, 116)	142 (125, 166)	**<0.001**
Calculated Annual Creatinine	101 (93, 115)	140 (125, 170)	**<0.001**
Hospital			0.8
AKUH	32 (28%)	10 (29%)	
KNH	84 (72%)	24 (71%)	
Duration of surgery (hours)			**0.04**
<=3.5	83 (77%)	20 (59%)	
>3.5	25 (23%)	14 (41%)	

[1] Signifies n (%); Median (IQR), [2] With Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

4.6 Risk factors of allograft dysfunction

Factors associated with kidney allograft dysfunction at 12 months were a history of AKI in the first year and duration of transplant surgery of more than 3.5 hours. Kidney transplant recipients were 13 times at risk of allograft dysfunction (p value 0.008) with an Adjusted Odds Ratio (AOD) of 13.2 (95% CI 1.98-88.1). Duration of surgery on the recipient longer than 3.5 hours was associated with 5-fold increase in risk of allograft dysfunction (p value 0.018 (95% CI 1.32-19.3).

The recipient male gender was associated with a non-statistically significant 4-fold risk of allograft dysfunction. When a KTR was discharged with a creatinine more than 132.6 µmol/l, it was associated with an increased risk that was however not statistically significant (AOD 2.57 (95% CI 0.77- 8.51) and so was receiving Methyl prednisone pulse therapy. This is summarized in table 4.5.

Table 4.5: Risk Factors of Allograft dysfunction

Characteristic	Estimate	Adj OR	Std. Error	p-value	LCI	UCI
(Intercept)	-6.050	0.002	1.340	0.000	0.000	0.000
Male Recipient Gender	1.452	4.272	0.755	**0.057**	0.958	19.049
Recipient Marital Status						
Married (Ref)						
Single	-0.448	0.639	0.709	0.529	0.155	2.627
Recipient history of pre-transplant blood transfusion	1.193	**3.296**	0.652	0.071	0.903	12.037
History of receiving Methyl prednisolone pulse therapy	0.796	**2.216**	0.639	0.217	0.623	7.885
Any documented AKI in first year	2.582	13.225	0.951	**0.008**	1.986	88.058
Creatinine level at discharge >132.6 µmol/l	0.945	**2.572**	0.604	0.121	0.777	8.508
Duration of surgery (hours) >3.5 hrs	1.623	5.067	0.675	**0.018***	1.328	19.337
Donor pre nephrectomy single kidney eGFR > 40 ml/min/1.73m^2	-0.192	0.825	0.842	0.820	0.152	4.482

Chapter 5: Discussion

In this study to assess kidney allograft function and its determinants in KTRs, we found a predominantly male donor population which agrees with other populations in the United Kingdom (UK) [57], United Network for Organ Sharing (UNOS) data[58] and Ivory Coast[59] but contrasts with our counter parts in South Africa[60] and Tunisia[61]. However, we share similar age range with a South African study where the average donor age was 35.2 years and another similar young population with an average age of 29.4 years in the Ivory Coast study. Living Kidney Donors (LKDs) are generally above 40 years of age in the UK, UNOS and Tunisia publications above.

Our average LKD BMI of 24.7 kg/m^2 and pre-nephrectomy total eGFR of 96 ml/min/1.73m^2 emphasize the fact that the study sites adhere to KDIGO guidelines for evaluation of the LKD[62].

A substantial number (85%) of donors were first degree relatives which suggests these are more knowledgeable about transplantation and its benefits[63], moreover, first degree relatives are more likely to be involved in education programs and screening than other relatives.

The most prevalent primary diagnoses in ESKD were hypertension and diabetes. Hypertension is a frequent associated factor and complication of ESKD[64] but is also a risk factor for the development of CKD [65]. Diabetes Mellitus also has been known to be an important cause of chronic kidney disease [66] and a risk factor of mortality among patients with CKD [67]. Our cohort echoes results from population studies done in Australia[68] and South Asia[69] and hospital studies done in South Africa[70] and Ghana[71].

Chronic glomerulonephritis usually clinically diagnosed in young patients with chronic kidney disease (CKD) coupled with an ultrasound scan suggestive of small shrunken kidneys and proteinuria. This can be suggested by the study median age of 36 years and an 85% prevalence of proteinuria on dipstick in the study. A large proportion of recipients had no documented primary kidney disease. The high prevalence of chronic glomerulonephritis is also seen in other populations in Cameroon[72] and Australia[68].

Allograft dysfunction in our study was present in 22.6% when defined as serum creatinine ≥132.6 μmol/l. To our knowledge this is the first study to describe this in the region. A retrospective study by Hariharan, S et al[29] followed up more than 100,000 cadaveric and living

donor transplants over 11 years and showed that progressive decline in graft half-life was associated with increments in one year creatinine. This study did not publish the prevalence of allograft dysfunction ,however, it was suggested that the serum creatinine at 12 months could be used as a surrogate marker of graft dysfunction since it could predict the latter[2] . Such short term surrogate markers can be used as end points in clinical trials to achieve cost reduction since follow up time is definitely shorter than other traditional end points like graft failure[30]. Kidney transplant recipients with kidney allograft dysfunction as defined in this study have a shorter allograft half-life of 14.5 years as opposed their normal counterparts whose half-life goes past 20 years[29].

Clinical presentation of KTRs with allograft dysfunction

When we compared demographic, clinical and biochemical characteristics in KTRs with normal kidney allograft function and kidney allograft dysfunction, male gender, a married marital status, history of pre-transplant blood transfusion, pulse therapy with methylprednisolone, AKI in first year of transplant, a high discharge creatinine and surgery above 3.5 hours were more prevalent at bivariate analysis with statistical significance.

The male gender has been associated with a poor health seeking behavior world-wide[73] and poor hypertension control post kidney transplantation in Kenya[74]. These two factors can partly explain the association with poorer graft function in this study. Poor health seeking behavior in men, as a study in Nigeria showed[75], does not depend on whether the person is educated or not. Unfortunately, the average blood pressures were not documented as part of this study and a thus, we cannot comment on its influence on allograft dysfunction.

Red Blood Cell (RBC) transfusion increases chances for Antibody Mediated Rejection (ABMR)[76] and allograft dysfunction because the packs may contain platelets and leucocytes that express HLA antigens[77] and increase risk of allosensitization; this could explain the association with allograft dysfunction and with time, this can lead potentially to graft loss if unchecked. Risk of sensitization can be reduced with use of leuco-depleted RBC transfusion with a marked reduction in ABMR episodes [78].

Treatment of T-Cell Mediated Rejection (TCMR) conventionally includes methyl prednisone therapy with 250 to 500mg once daily over 3 days as directed by guidelines[28], occasionally in limited resource settings, when all causes of an acute graft dysfunction have been ruled out, the clinician prescribes the therapy as empirical treatment for a possible rejection. The close

association of this therapy and allograft dysfunction suggests that this could indeed have been true rejection. Rejection episodes increase the likelihood of dysfunction through injury to the graft and its microcirculation[79].

Transplant patients have numerous risk factors for AKI mechanisms of which differ but the end result is an injured allograft vasculature and or tissue. AKI was found to predict graft failure in a single center retrospective study of 289 LDTs in Japan after a four-year duration of follow up[80]. Indeed, before allograft failure occurs, dysfunction precedes and as thus; more KTRs with allograft dysfunction were more likely to have had an episode of AKI in our study.

The KTRs with a discharge creatinine more than or equal to 132.6 umol/l had higher chances of having a dysfunctional allograft. This has also been shown in the UNOS data[81] and a Cuban study[82] where higher creatinine levels increased chances of poor outcomes. More recent data shows that because most transplant recipients have not reached their nadir creatinine levels by discharge, this may be misleading.

The median duration of surgery in this study was 3 hours which agrees with literature in the UK[83]and the US[84]. In our study, surgeries that lasted more than 3.5 hours were associated with allograft dysfunction. Surgery quality has an impact on outcomes of kidney transplant[85] and indeed the longer the surgery for whatever reason, the longer the allograft is exposed to ischemia reperfusion injury (IRI)[86] that has been shown to cause allograft dysfunction and predispose to early rejection[87].

Risk factors of allograft dysfunction

Risk factors of allograft dysfunction at 1 year in our study were AKI in the first year (p value 0.008) and duration of transplant surgery of more than 3.5 hours (p value 0.018). Other variables that had an increased risk but were statistically non-significant were the male gender ((P value 0.057 AOD 4.3 (95% CI 0.96-19.04)), history of pre-transplant blood transfusion ((P value 0.07, AOD 3.3 (95% CI 0.47-2.01)), serum creatinine level at discharge more than 132.6 µmol/l ((p value 0.121, AOD 2.57 (95% CI 0.9-12.04)) and history of receiving methyl prednisone pulse therapy ((p value 0.217, AOD 2.22 (95% CI 0.62-7.88)).

Acute Kidney Injury is a common problem at different stages post transplantation. In our study, 55% of recipients had a documented AKI episode within the first year of transplantation as defined by a ≥1.5 times increase in serum creatinine from previous known value. The post-transplant patient is at risk of AKI due to the state of CKD, calcineurin inhibitors, infections[88]

and rejection [89]. AKI in the post-transplant can thus be asymptomatic such as in the case of rejection and BK virus nephropathy or symptomatic in the case of full-blown infection. In our study, 25% of recipients had sepsis during the peri transplant period and 41% were diagnosed with an infection within the first year after transplant, most commonly urological infections such as Urinary Tract Infection. In non-transplant patients, the hemodynamic alterations, endothelial and cellular injury associated with AKI is repaired to varying degrees in different patients, making AKI a risk factor for CKD [90]. In the KTR, this would manifest as allograft dysfunction. Indeed, AKI after transplant has been documented as a risk factor for allograft failure by Nakamura and colleagues who studied 289 LDTs in Japan [91]. The negative impact of AKI on transplant outcomes reaches out also to non-kidney transplantation as seen in the study by Paolo and colleagues in patients of liver transplantation [92].

In our study, surgeries that lasted more than 3.5 hours were associated with allograft dysfunction. We hypothesize that the long duration of surgery exposes the allograft to more IRI[86]. The IRI usually leads to a nonspecific inflammatory response that can eventually compromise graft viability. Hailin Zao and colleagues suggest that this cascade of events can lead to later graft dysfunction and loss by causing graft vascular injury, a chronic hypoxic state and in some cases a reduction of renal function mass[87].

Conclusion

This study has shown that allograft dysfunction is present in about a quarter of our transplant population by one year. Risk factors included acute kidney injury and undergoing surgery for more than 3.5 hours.

Limitation

This was a retrospective study and had inherent issues of missing data. We countered this, however, by using two centers hence increasing records available for analysis.

We used convenient sampling to choose the two study sites, this may create a selection bias, however, all charts were reviewed to reduce this bias. Multiple Imputation statistics method was used to help create a model for multivariate analysis. Also using creatinine for allograft function assessment focuses mainly on excretory function and this could miss out on other parameters like filtration dysfunction in early recurrence of the primary disease. It is however reproducible and easily measurable.

Recommendations

1. One in two patients get a blood transfusion before, during and around transplantation; this sheds light on the need for optimization of management of anemia in our CKD population. Timely assessment and intervention for cause of anemia and use of Erythropoiesis Stimulating Agents and Iron therapy where indicated should be optimized to reduce and finally avoid use of red cell transfusions
2. Prompt recognition, evaluation and management of AKI in the post-transplant patients is key, to improve long term outcomes of transplantation.
3. Follow up studies could look at
    a. A study to describe recipients further and look at other outcomes of transplant including graft loss, death with functioning graft and graft half-life.
    b. A longitudinal study to get a proper casual correlation for AKI and surgery duration to graft dysfunction and/or loss
    c. Follow up study to assess the impact of the allograft dysfunction at 12 months defined in this study on long term outcomes
    d. Comparison of Donor Specific Antibodies' prevalence between recipients who received red cell transfusion compared to those that did not and its impact on outcome

APPENDICES

Appendix 1: DATA EXTRACTION TOOL

(Questionnaire for determinants of kidney allograft function at one year post transplantation at two centers in Kenya)

Serial No: ……

A. DEMOGRAPHICS OF RECIPIENT:

1. I.P. No: ……..
2. Age (yr): ……
3. Gender (M/F): …….
4. Tribe: ……
5. Residential county: …….
6. Marital status: Single/Married/Divorced/Separated

B. DEMOGRAPHICS OF DONOR

7. I.P. No: ……..
8. Age (yr): ……
9. Gender (M/F): …….
10. Tribe: ……
11. Residential county: …….
12. Marital status: Single/Married/Divorced/Separated
13. Relation to recipient: Parent/ Sibling/1st degree relative/second degree relative

C. CLINICAL DATA OF RECIPIENT

14. Primary kidney disease:

……

……

15. Co-mobidities:

……

……

……

……

…….

16. Calculated dialysis vintage (Months): …….

17. History of smoking: ……

18. History of pre-transplant blood transfusion: ……..

19. History of peri-transplant blood transfusion: …….

20. Immediate pretransplant weight (Kg): …….

21. Immediate pre-transplant height (M): …….

22. Calculated BMI (Kg/m^2): ……..

23. Urine protein (absent/present): ……..

D. CLINICAL DATA OF DONOR

24. History of smoking: ……

25. Pre-existing illness (specify):

……

…….

26. Immediate pretransplant weight (Kg): …….

27. Immediate pre-transplant height (M): …….

28. Calculated BMI (Kg/m^2): ……..

29. Pre nephrectomy total eGFR (ml/min/1.73m^2):

……

30. Pre nephrectomy single Kidney eGFR (ml/min/1.73m^2):

    …….

31. Donor Kidney side: ……..

32. Donor renal artery number (single/multiple):

    …….

E. HLA Mismatch:

33. Total mismatch: ……

34. HLA – A mismatch: …….

35. HLA – B mismatch: …….

36. HLA – DR mismatch: …….

F. PERI TRANSPLANT DATA

37. Induction therapy used

    a. Steroids: ……

    b. Mycophenolate Mofetil: …….

    c. Calcineurin Inhibitor: ……

    d. Basiliximab: ……

    e. Anti-thymocyte globulin (ATG): …….

    f. Other: …….

38. Cold ischemic time (minutes): ……..

39. Warm Ischemic time (minutes): …….

40. Duration of surgery (hours): …….

41. Surgical complication (Clavien Dindo classification): ……

42. Documentation of sepsis: …….

43. Documentation of hypotension during transplant admission: ……

G. POST TRANSPLANT DATA

44. Length of hospital stay (days): ……

45. Creatinine level at discharge (umol/L): ……..

46. Specific infection diagnosed in first year:

……

47. History of receiving Methyl prednisolone pulse therapy: …….

48. Any documented Acute Kidney Injury (AKI) in first year:

……

49. Average CNI level for the 12 months: ……

50. Creatinine level at one month (umol/L): ……

51. Creatinine level at third month (umol/L): ……

52. Creatinine level at 6^{th} month (umol/L): ……

53. Creatinine level at 12^{th} month (umol/L): ……

54. Calculated Δ Creatinine (umol/L): …….

Appendix II: The Clavien-Dindo Classification of surgical procedure complications

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) * requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multi organ dysfunction
Grade V	Death of a patient

**brain hemorrhage, ischemic stroke, sub-arachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.*

Appendix III: Results from multiple imputation

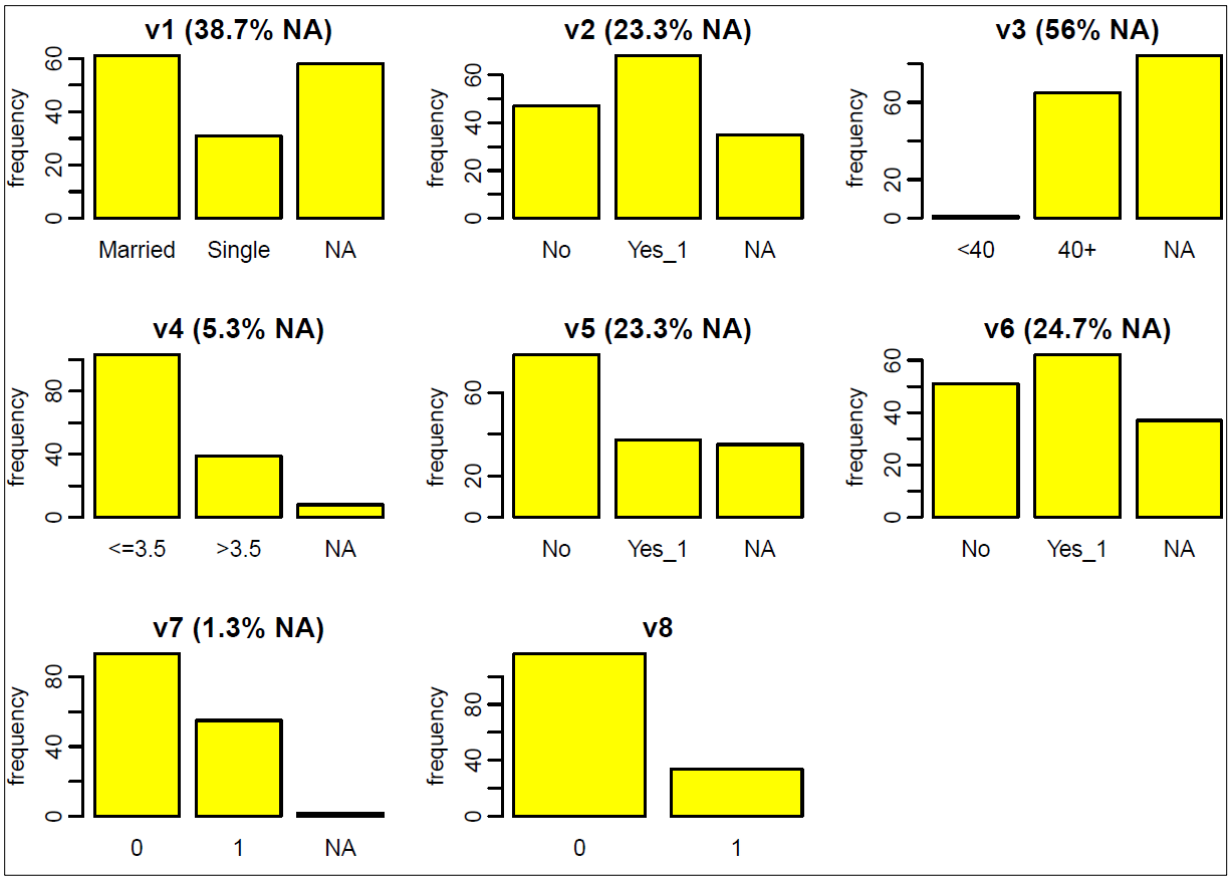

Figure A.7: Proportion of missingness in the key variables

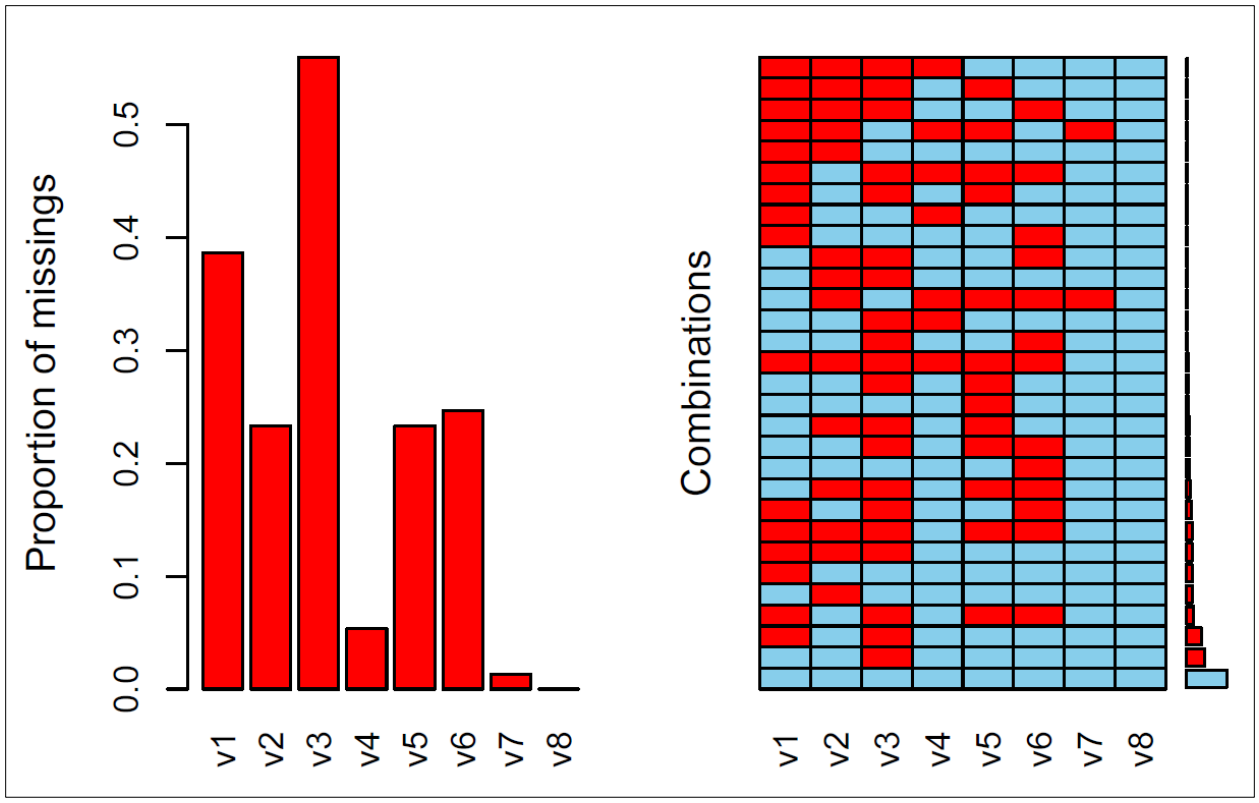

Figure A.8: Proportion of missingness and missingness combinations

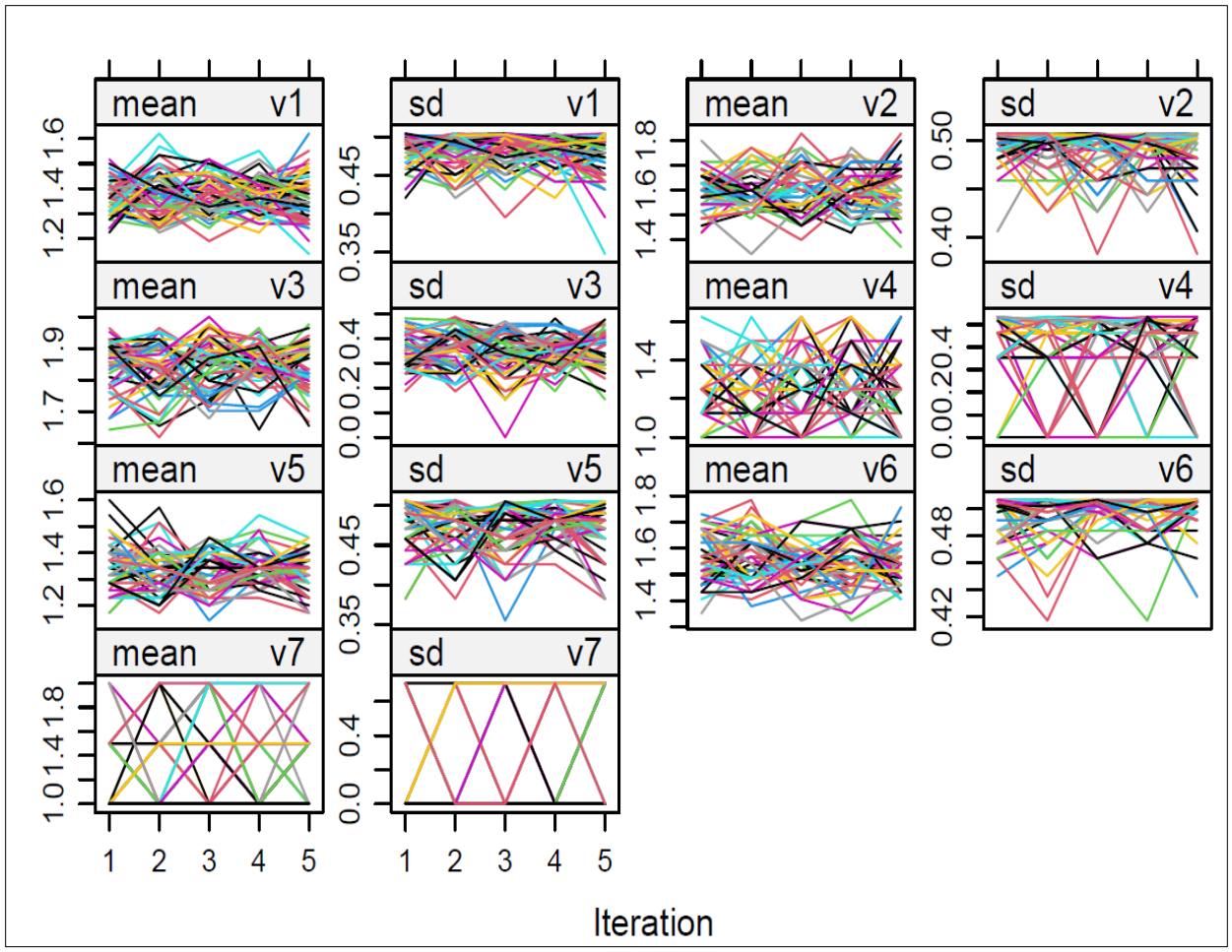

Figure A.9: Divergence by Iteration after multiple imputation

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