PREDICTORS AND OUTCOMES OF ALLOGRAFT DYSFUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT MUHIMBILI NATIONAL HOSPITAL

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PREDICTORS AND OUTCOMES OF ALLOGRAFT DYSFUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT MUHIMBILI NATIONAL HOSPITAL

By

BATANYITA, Julieth Antony

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine in Internal Medicine of Muhimbili University of Health and Allied Sciences
October, 2017
CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: “Predictors and outcomes of allograft dysfunction among kidney transplant recipient at Muhimbili National Hospital” in (partial) fulfillment of the requirements of the degree of Master of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences.

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Date

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Professor Eden. E. Maro
(Co – Supervisor)

__________________________________
Date
DECLARATION AND COPYRIGHT

I, BATANYITA, Julieth I declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…………………………………… Date……………………………………

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I would like to thank my classmate for their moral support and advice through this journey.

Last but not least my deep gratitude to my family for when I was to be a daughter, wife, a mother or sister some time I was I student first and they supported and compromised.
DEDICATION

To my spouse Elifadhili and our children Sandra and Robert.
ABSTRACT

Background: Kidney transplantation is a Renal Replacement Therapy modality of choice for ESRD. Renal allograft loss remains an area of concern. In most native kidney diseases, glomerular filtration rate (GFR) declines progressively over time in renal transplant recipients. Monitoring changes in GFR is the recommended method for assessing the progression of kidney disease, aiming at delaying graft loss and maximize graft survival by identifying and deterring modifiable factors.

Rationale: Identifying predictors of poor allograft function will help clinicians in selecting donor-recipient pairs that will maximize allograft survival as well as patients’ survival and quality of life. No study on the subject has been done in our country and there is tendency of some patients to return to chronic dialysis within a year of transplant. Hence this study was set to determine predictor of allograft dysfunction among renal recipients.

Methodology: Conducted a retrospective study at the Renal Transplant Clinic at Muhimbili National Hospital (MNH). Attendees of the clinic are patients who underwent renal transplantation abroad as of current transplant services are not available in the country. The Renal Transplant Clinic at the MNH runs a live-related donor Pre-Transplant Clinic and a lifelong follow-up for post kidney transplant recipients. A total of 182 recipients who were transplanted with minimum of at least 3 months post-transplant were included in study. Using questioner factors at time 0, 3,6,12 month post-transplant such as recipients’ and donors’ BMI, gender, proteinuria, eGFR change, elevated blood pressure and episode of allograft rejection were recorded and MDRD to asses for eGFR. All these factors were obtained from patients’ files supplemented with discharge summary from transplant center. The association between graft function and predictors was assessed by logistic regression. Outcome variables were; development of ESRD, return to dialysis, repeat Transplant, allograft dysfunction (defined as eGFR<60ml/min/1.73sqm or death with a functioning graft. Factors with P-value < 0.05 was considered significant.
Results: Of 182 recipients, 146 (80.2%) were males. The mean age was 44.5(±12.5) years. Among donors, 97 (53%) were males with mean age of 35(±9) years whereby three quarters of the donors, 130(71%) were first degree relatives. Prevalence of allograft dysfunction at one year was 37.4%. Eleven recipients (6%) died with functioning graft within the first year of kidney transplant. On regression model; systolic blood pressure (SBP) of ≥140mmHg, proteinuria, and change of GFR emerged as significant predictors of allograft dysfunction.

Conclusion: The burden of allograft dysfunction in the 1st year of kidney transplantation is high among patients attending post-transplant clinic at MNH. Monitoring post-transplant blood pressure, proteinuria and rate of change in GFR can help in regressing graft dysfunction following transplant.

Recommendation: Timely and good post-transplant care on altering risk factor of graft dysfunction will increase graft and patient survival.
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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADPKD</td>
<td>Adult Polycystic Kidney Disease.</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immune deficiency Syndrome</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DGF</td>
<td>Delayed Graft Function</td>
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<td>DM</td>
<td>Diabetic mellitus</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<td>ESRD</td>
<td>End Stage Renal Disease</td>
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<tr>
<td>Hb</td>
<td>Hemoglobin</td>
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<tr>
<td>HbA1c</td>
<td>Glycated Hemoglobin</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>LKD</td>
<td>Living Kidney donor</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<tr>
<td>MNH</td>
<td>Muhimbili National Hospital</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NHIF</td>
<td>National Health Insurance Fund</td>
</tr>
<tr>
<td>NKF</td>
<td>National Kidney Foundation</td>
</tr>
<tr>
<td>NODAT</td>
<td>New onset of diabetes after transplant</td>
</tr>
<tr>
<td>OPTN</td>
<td>Organ Procurement and Transplantation Network</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>RRT</td>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
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<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing</td>
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</table>
DEFINITION OF TERMS

Renal transplant is a surgical procedure which places a functioning kidney from a donor into a person whose kidneys no longer function properly.

Acute allograft dysfunction is defined as an acute deterioration in allograft function associated with specific pathology changes in graft.

A chronic allograft dysfunction is defined as functional and morphological deterioration of renal allograft at least 3-6 month after transplant. In this study, the operational definition for allograft dysfunction is eGFR <60ml/min/1.73m$^2$, documented allograft rejection, return to Hemodialysis after Transplantation, death with functioning graft.

Proteinuria: serial of 2 or more urinalysis with ≥1+ on a standard urine dipstick or urinary protein excretion of greater than 150mg per day in absence of UTI.

Hypertension: According to National institute for health and clinical excellence (NICE) criteria - Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on three readings or if patient is known to be hypertensive or is on treatment for hypertension.

UTI: an infection of one or more structures in the urinary system it can include cystitis, pyelonephritis, and urethritis. In this study, UTI will be defined as presumptively.

By definition: Presumptive diagnosis of UTI will be considered as urinalysis findings of >5 WCC/hpf, Positive results for leukocyte esterase and nitrates, presence of RBC in urine with or without symptoms of lower urinary tract infection.

Study cohort: Renal post-transplant patients.
CHAPTER ONE

1.0 INTRODUCTION

1.0.1 Background

Chronic Kidney Disease

The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) of the United States of America (U.S.A) defines chronic kidney disease as kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m$^2$ for 3 or more months. Markers of CKD include: proteinuria, haematuria and/or abnormal renal imaging. As serum creatinine may not accurately reflect kidney function, GFR is estimated (eGFR) by calculation such as the Modification of Diet in Renal Disease (MDRD) formula$^1$

There is increasing incidence of kidney disease with ESRD globally and sub-Saharan Africa in particular. Chronic kidney mostly due to hypertension and glomerular diseases affects mainly young adults aged 20–50 years in sub-Saharan Africa, while in developed countries it presents in middle-aged and elderly patients, diabetes mellitus and hypertension being the leading causes$^2$. The estimated increase in diabetes mellitus in Africa is anticipated to be 12.7 million, an increase of 140% by 2025$^3$.

In Tanzania the prevalence of ESRD is estimated to be 3.5% with the prevalence of chronic kidney disease (CKD) of 7.0%$^4$. DM prevalence in Tanzania in 2012 was about 9.1%, as documented in 2012 Tanzania national survey (WHO 2012).

Knowledge on the etiology of kidney disease is essential because the primary renal pathology may influence the outcome with respect to the possibility for recurrence of disease and the association of comorbidities. Moreover knowledge on predictors of kidney disease could salvage the graft at risk.
Treatment of Chronic Renal Failure

Renal replacement therapy is limited in most of sub-Saharan Africa due to high costs and lack of available therapy resulting in the high rate of morbidity and mortality. Renal replacement therapy was accessed by approximately 1.8 million people worldwide in 2004 and only 5% of the dialysis population was from sub-Saharan Africa. The cost of dialysis by 2014 in Tanzania per single session of hemodialysis was about 176 US$. Thus, an average patient requiring three dialyses per week (i.e. 156 dialyses per year) would require a total of 27,440 US$ per annum.

Kidney Transplant.

Kidney transplantation is a surgical procedure which places a functioning kidney from a donor into a person whose kidneys are no longer functioning. The first human to human kidney transplant was performed in 1933, possibly due to ABO incompatibility the graft lasted for only 4 days. The first successful living donor renal transplant was between identical twins. Whereas the first Tanzanian received renal transplant in 1981 in London.

Kidney transplantation is the Renal Replacement Therapy (RRT) modality of choice for ESRD. Compared to dialysis therapy, it provides better quality of life and improves survival. Renal allograft dysfunction following transplant is a common problem and appropriate post-transplant care is crucial for the long-term graft function and graft survival. As in most native kidney diseases, GFR declines progressively over time in renal transplant recipients. Several studies have shown that the decline of renal function can be calculated beyond 6 or 12 months after transplantation.

There are two types of allograft dysfunction acute and chronic risk factors include immunological and non-immunological e.g. CNI toxicity, obstruction (thrombosis or prostate), hypertensive nephrosclerosis, recurrent or de novo glomerular disease, cellular and/or, humor rejection respectively.
The two main factors associated with long-term renal allograft loss have been found to be death with a functioning graft and chronic allograft nephropathy (CAN). The later was found to be the leading cause of late renal allograft loss. Following transplantation, patients are put on immunosuppressants so as to prevent graft versus host reaction which may lead to graft rejection. Transplant between non-identical donor-recipient pair has become successful due to presence of immunosuppressants which reduce the risk of rejection. Thus with increase in demand for live kidney donors, it is important to ensure long-term survival of kidney allograft. Monitoring changes in glomerular filtration rate (GFR) is the one of recommended method for assessing the progression of kidney disease.

Whatever methods are used to assess graft wellbeing, aim is to delay graft loss and maximize graft survival by assessing and manage risk factors.

**Monitoring of Post-Transplant Patient**

The most important goal of short-term and long-term medical follow-up is to enable noting signs and symptoms of renal allograft dysfunction. Renal parenchymal dysfunction has many causes including rejection; nephrotoxicity of calcineurin inhibitors or recurrence of native kidney disease hence systematic approach can alter the progression. Therefore kidney transplant recipients must be carefully monitored so as to ensure the health of the transplanted kidney and to lookout for complications of transplantation and immunosuppressive therapy.

Although measurement of serum creatinine (SCr) levels can assess renal function, the use of glomerular filtration rate (GFR) prediction equations has been found to be a valuable tool for more precisely quantitative post-transplant renal function. Modification of Diet in Renal Disease Study Group equation using SCr, age, gender, and race being prefered. Transplant renal biopsy may be required and is believed to be gold standard.
Monitoring blood levels of immunosuppressant drugs in order to avoid nephrotoxicity and ensure sufficient therapy is crucial. Calcineurin inhibitors (CNIs) such as tacrolimus (TAC) and cyclosporine (CsA) are a component of almost all immunosuppressive regimens, and their levels must be monitored closely, especially in the first year after transplantation, mainly due to their narrow therapeutic index. Furthermore, nephrotoxicity can be difficult to distinguish from rejection episodes\textsuperscript{19,20}.

**Follow up Guidelines for Kidney Transplantation**

Patients who have undergone kidney transplantation requires a long term follow-up for monitoring of the graft function as well as toxicities related to immunosuppressant. Guidelines recommends prior to each clinic visit, patients should have the routine blood work done including\textsuperscript{21}

- CBC (Hgb, platelets, WBC, differential)
- Potassium, Sodium, Chloride, Calcium, Phosphate.
- Glucose (fasting)
- Creatinine, urea
- Total and direct bilirubin
- Liver enzymes – alkaline phosphatase, ALT, AST
- Albumin

Immunosuppressive drug levels: Cyclosporine blood concentrations taken two hours post cyclosporine dose (C\textsubscript{2}) are preferred for patients on cyclosporine while trough levels are required for patients on tacrolimus and sirolimus

Fasting Blood Sugar and HgA\textsubscript{1c}: In the first 6 weeks post-transplant all patients should have fasting blood glucose done and then at least every 3 months. HgA\textsubscript{1c} is indicated to all diabetic patients every three months.
Lipid studies: These need to be done every 6 months post-transplant (total cholesterol, LDL, HDL and triglycerides).

Urine tests: Routine urine culture and sensitivity (C and S) test, urinalysis and urine albumin creatinine ratio / 24 hour urine are recommended. If results are abnormal, then follow-up tests may be done at more frequent intervals.

**Outcome of Kidney Transplant**

There is significant improvement on mortality and morbidity of post renal transplant recipients when compared to CKD patients on dialysis or not. Recently the prognosis after kidney transplantation has improvement, patients survival following cadaveric grafts is >73% after five years while for living donor it is > 84 % after 5 years\(^\text{22}\) and this has caused a dramatic increase in patients who are on waiting list as many dialysis patients turn to transplant\(^\text{22}\). In Europe in 1970s, the mortality of post renal transplanted patients who were 40 years and below was 35% and it kept increasing with age\(^\text{22}\).

Studies have shown if death with a functioning graft is not considered, the majority of late graft loss are due to chronic allograft nephropathy (CAN), previously called chronic rejection.\(^\text{23, 24}\).
1.1 Literature Review

Predictors of Outcome of Kidney Transplant

Various factors have been shown to have impact on short-term graft survival. These factors include delayed allograft function, human leukocyte antigen (HLA) antibodies, type of donor kidney, donor illness, and medical center factors. While factors that have impact on long-term graft survival include factors such as donor age, cause of prior ESRD, duration of dialysis and factors after the transplant such as proteinuria, type of immunosuppressant used, other medication used such as antihypertensive, serum creatinine, blood pressure and patient compliance.

Recipient Factors:

Recipient age

Recipient’s age is currently not considered an absolute contraindication for renal transplantation. Various studies have shown with advanced age death with functioning renal graft is more common occurring at a rate of 1.1/100 patient years in young recipients and at 4.1/100 patient years in recipients older than 65 years. Factors contributing to higher risk of comorbidities in this age group include cardiovascular disease, infections and malignancies. Hence survival at 5 years is 93% in recipients <60 years, but only 72% in recipients >60 years.

Body Mass Index (BMI)

Independently, obesity has been associated with other conditions such as hypertension, hyperlipidemia, type II diabetes, proteinuria and glomerulopathy. Therefore it is possible that renal transplant recipients who have elevated BMI are at risk of inferior graft survival due to these factors. Moreover elevated BMI was found to be associated with an increased risk for delayed graft function hence increase the risk of allograft nephropathy/dysfunction. Furthermore study have shown Post-transplant patients gained average weight of 3kg in the first post-transplant year and post transplantation weight gain and obesity have been
associated with decreased long term allograft and patient outcomes\textsuperscript{31,32}. Risk group for post-transplant weight gain being, female, young, black and low-income patients with type 2 diabetes\textsuperscript{33}.

**Duration of dialysis prior to transplant**

Duration of dialysis prior to transplant has been shown to have impact on recipients graft survival. Whereby those who had dialysis before transplant and those who had preemptive transplantation of kidneys from living donors the latter was associated with longer allograft survival\textsuperscript{34}. When compared to preemptive transplants, waiting times of 0 to 6 months, 6 to 12 months, 12 to 24 months, and over 24 months confer a 17\%, 37\%, 55\%, and 68\% increase in risk for death-censored graft loss after transplantation, respectively\textsuperscript{35}.

The association between increased duration of dialysis before transplantation and increased probabilities of acute rejection by six months is supported the concept of an immunologic effect of dialysis\textsuperscript{36}. As it has shown that dialysis has effect on immunological improvement of T-cell proliferation and hence not having dialysis was associated with that impairment in the immune system response and therefore patient who underwent dialysis were at risk of acute rejection\textsuperscript{37,38}.

**Renal function**

The parameters of renal function mainly serum creatinine; creatinine clearance and glomerular filtration rate (GFR) are valuable indicators of long-term outcome\textsuperscript{39}.

In the multicenter studies; on renal transplant recipients a lower rate of GFR decline was associated with absence of rejection. Hence follow up on renal function enables identification of patients at highest risk of graft failure and provide a vital tool for improving outcomes\textsuperscript{40}. 
**Blood pressure**

Normal blood pressure is defined as 120/80 mmHg by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure and the K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in CKD.\(^{41}\)

The American Society of Transplantation (an older guideline) recommends target blood pressure levels of <140/90 mmHg\(^{42}\). The European Best Practice Guideline recommend mandatory blood pressure control to levels of <130/85 mmHg in kidney transplant patients without proteinuria and <125/75 mmHg in patients with proteinuria.\(^{43}\) Based on this definition, the incidence of post transplantation hypertension ranges from 50% up to 80%. There are various causes of post transplantation hypertension including calcinerium inhibitors (CNI) use, prednisone, preexisting hypertension, primary kidney disease, kidney transplant artery stenosis, and graft dysfunction.\(^{44}\)

Independently systolic and diastolic hypertension is a risk factor for both graft and patient loss in kidney transplant recipient\(^{45}\) it has been associated with atherosclerotic cardiovascular disease, which in turn can cause of premature death and a major factor in death-censored graft failure in transplant recipients. Hence hypertension monitoring on its possible causes and complication is essential for patient and graft survival\(^{46}\). A recent analysis of the Collaborative Transplant Study showed that lower systolic blood pressure, even after the first post-transplant year, was associated with improved graft and patient survival\(^{47}\).
Proteinuria
It has been shown that proteinuria from the native kidneys normally resolves within the first 1 to 10 weeks post transplantation\(^{48}\). The incidence of proteinuria in kidney transplant patients ranges between 10 and 25\%\(^{49}\).

Independently proteinuria has shown to be associated with an increased risk of renal failure. Post-transplant proteinuria affects not only graft survival but also patient survival\(^{50}\). It plays part on renal transplant dysfunction and fibrosis through abnormal proximal tubule protein uptake and tubular cell toxicity\(^{51}\).

Moreover a study by Guijarro showed that following renal transplant, hypoalbuminaemia is common, and is a strong independent risk factor for morbidity and mortality including infection\(^{52}\). Therefore it is important for renal transplant patients to be evaluated for proteinuria following transplant regularly\(^{53}\).

Prior cause of ESRD
Knowledge on the etiology of renal disease is important because the primary renal pathology may have predisposition to recurrence of disease and the association of comorbidities.

The possibility of recurrence varies, it is greater in FSGS, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), hemolytic-uremic syndrome (HUS), than with lupus nephritis, anti-glomerular basement membrane (GBM) disease and vasculitis.\(^{54}\). Furthermore timing of recurrence and mode of presentation following transplant differ with different condition, can be as early as weeks as in FSGN or after first year of transplant as in diabetics\(^{55}\).

Studies have shown the incidence of Glomerulonephritis (GN) recurrence post transplantation to range between 6 and 19.4\% and may result in graft loss in almost 8.4\% of cases\(^{56,57}\).

A study on both native kidney and kidney allograft biopsies on cases documented to have recurrent glomerular disease, graft loss due to recurrence of primarily diseases showed glomerulonephritis to be the third most common cause for graft failure 10 years after kidney
transplantation. Therefore it is important to suspect GN in individuals with proteinuria, hematuria, and deterioration in allograft function after the first year since it is associated with increased risk for graft loss.

**Hepatitis C**
HCV possibly because of increased HCV RNA titers that result from immunosuppression is believed to be associated with more frequently glomerular disease in the renal allograft compared with native kidneys. HCV infection have been associated with membranous glomerulonephritis, and MPGN as a principal cause of de novo GN in renal allografts.

**Diabetes**
World Health Organization and the American Diabetes Association definitions of diabetes and impaired glucose tolerance are used to define New-Onset Diabetes after Transplantation (NODAT). Its prevalence increases with time. It occurs in 25% of kidney transplant recipients and is likely to decreases patient and/or graft survival. Its risk factors, include Immunosuppressive therapy with tacrolimus, prednisolone older recipient age more than 45 years, hepatitis C, rejection episodes, black race, and higher body weight.

**Donor Factors**

**Donor age**
Donor age has been found to be one predictor of long-term renal allograft function; possibly due to the decrease in the absolute number of functioning glomeruli with age, and graft outcome from kidney transplantation from elderly donors are found to be inferior to those from young donors.

The study by Kumar et al. on older donor renal biopsy performed found; glomerulosclerosis in 85% samples, patchy interstitial fibrosis in 64%, thickening of the arteriolar wall and mesangium in 47%, chronic inflammatory cells in the interstitium in 29% and cystic changes in 6% of the kidneys. Moreover study showed a decline in GFR was more on the person above
55 years aged emphasizing than younger kidney donor. In other study delayed graft function which had effect on graft function was more on advanced aged donor.

**Donor – Recipient Factors**

**HLA matching**

All transplant recipients and their prospective donors undergo tissue typing to determine the HLA matching whereby; 6 HLA antigens are determined. The mismatched at each of the HLA loci define degree of incompatibility between the donor and the recipient and mismatches increase the risk of rejection. As observed grafts from HLA identical siblings survive longer when compared to HLA-mismatched grafts from siblings or unrelated donors.
1.2 Problem Statement
In this current era non-communicable diseases are on rise in Sub-Saharan Africa including Tanzania. Among these are hypertension and diabetes mellitus which are leading causes of ESRD worldwide while in developing country is glomerulonephritis\textsuperscript{72,73}. Since the best option of renal replacement therapy is renal transplantation\textsuperscript{74,75} and the fact that the number of patients receiving renal transplantation has been steadily increasing, a proper follow up of renal recipient is crucial for preserving recipient wellbeing as well as donor right. If proper evaluation of recipient is not observed the risk of developing allograft dysfunction becomes high.

The first live kidney donor (LKD) transplantation for a Tanzanian patient was done in 1981 in London\textsuperscript{76} and since then about 270 patient have been transplanted. The main donor source being biological relatives. The other sources includes cadaveric and spouse. For the last one year approximately 28 pairs of donor: recipient have been sent abroad mainly India for renal transplant.

Post-transplant patients face long term complications either due to graft rejection or due to complications of immunosuppressants as a result of immune suppression/infections or due to other side effects of medication. Moreover graft failure can result from either poor adherence of immunosuppressant, due to recurrence of the disease which caused CKD or poor compatibility with donor. Thus in the long run reduced eGFR either reversible or non-reversible can result as a common endpoint of allograft dysfunction resulting from whatever cause.
1.3 Rationale
There is limited available data on the wellbeing of post kidney transplant patients in Tanzania despite an increase in the number of post-transplant kidney patients over the past ten years. Few previous studies in Tanzania have assessed the clinical and laboratory profiles of the kidney recipients; but no study is documented to determine predictors and outcome of allograft dysfunction among kidney transplant recipients.

To improve post-transplant outcome, development of prevention programs and increasing funding on donor workup, recipient post-transplant care such as immunosuppressants, and screening tools is important to ensure increased availability of successful RRT. To achieve this, we need to know the profile of those who have already been transplanted and their post renal transplant outcomes.
Moreover by studying and understanding allograft dysfunction and its predictors among kidney transplant recipients, I expect to enlighten on the extent of allograft dysfunction, major etiologies of allograft dysfunction and outcome and predictors, among these patients. These findings will guide on drafting prevention strategies such as donor recipient matching, aiming at reducing the burden of allograft dysfunction/loss. This knowledge will emphasis insight to clinicians who may intervene appropriately and timely and consequently optimize post-transplant graft function such as we could try reduce combination of high risk factors in recipients.

1.4 Research questions
(a) What are the characteristic of renal recipient and donor?
(b) What is the magnitude of allograft dysfunction among post-transplant patients?
(c) What are common predictors of allograft dysfunction among post-transplant patient?
(d) What are the outcomes of allograft dysfunction among post-transplant patient?
1.5 Objectives

1.5.1 Broad Objective
To determine predictors and outcomes of allograft dysfunction among kidney transplant recipients attending renal transplant clinic at MNH.

1.5.2 Specific objectives
   (a) To describe the socio-demographic characteristics of kidney transplant recipients attending renal transplant clinic at MNH.
   (b) To determine the prevalence of allograft dysfunction (eGFR-based) among kidney transplant recipients attending renal transplant clinic at MNH.
   (c) To determine predictors of allograft dysfunction among kidney transplant recipients attending renal transplant clinic at MNH.
   (d) To determine outcomes (return to dialysis, repeat transplant, death) of allograft dysfunction among kidney transplant recipients attending renal transplant clinic at MNH.
CHAPTER TWO

2.0 METHODOLOGY

2.1 Study Design
This study was a retrospective cohort.

2.2 Study Site
The study was conducted at the renal transplant clinic at Muhimbili National Hospital (MNH). MNH is a tertiary referral and teaching hospital, situated at Upanga in the city of Dar es Salaam. The hospital serves patients referred from other regional hospitals in the country including Ilala, Temeke and Mwananyamala municipal hospitals. It has a bed capacity of approximately 1,500 and serves about 1,500 outpatients per day. In Tanzania; MNH is the only hospital where there is work up for prospective kidney donors and provides care for both kidney donors and recipients after the transplant operation has been performed outside Tanzania (largely in India). Of recent approximately 20 donor and recipient pairs are going abroad for transplant under government sponsorship per year.

The renal transplant clinic is well-established since 2009 and is located on the ground floor of pediatric complex building. Among 276 renal recipients on registry 226 patients are attending MNH transplant clinic of whom those meting criteria of inclusion that is having more than three month duration post-transplant and accessible data are 182. It has good file records and
assures easy file retrieval as the clinic keep its files within the clinic. The clinic is open every day in case of emergency although post-transplant clinic is conducted once a week on every Monday attending about 25 patients per day.

Patients follow up schedule is individualized. On the first year of transplant patients are seen initially every week then at least every month with the frequency of visit decreasing as time to post transplant increases. Patients should have been reviewed at least once a year no matter how stable the patient is.

On every visit patients are monitored for renal function test by assessing serum creatinine and urea, hematological monitoring including full blood count for signs of infections, urinalysis for evidence of protein in urine and signs of infections. They also monitor blood pressure, blood glucose and body weight as increases in these have effects on kidneys.

2.3 Study Population
All achieved data of kidney recipients attending transplant clinic at Muhimbili National Hospital with a minimum of 3 months post renal transplant period.

2.4 Study Duration
The study was conducted for 6 months, from September 2016 to February 2017.

2.5 Inclusion Criteria
All complete filled case-files of kidney recipients with minimum data of 3 month duration post-transplant.

2.6 Sampling technique.
Archived files were enrolled in consecutive manner at time of data collection.
2.7 Data Collection Procedure
List of transplanted patients was obtained from post renal transplant data base. From the list patient’s name and file number was identified and their files retrieved from renal unit records. A structured questionnaire was used to collect data. Patients’ data collected included age, gender, primary/pre-transplant renal disease, duration on dialysis, type of dialysis before transplant, height and weight, serology to hepatitis C and B virus, CMV and HIV , while for donors data collected were age, gender, type of donor, and BMI, grafts human leucocyte antigen (HLA) mismatches, immediate graft function, rejection episodes and immunosuppression]. Clinical and biochemical variables (hemoglobin, serum creatinine, proteinuria, blood glucose, serum lipids) were collected at 0, 3, 6 months and 12 months.

Immunosuppressive treatment were recorded at each visit and classified into three groups: (i) cyclosporine based, (ii) tacrolimus-based and (iii) calcineurin inhibitor (CNI)-free therapy.

Post-Transplant recipients and graft: Outcome variables: eGFR at study times (MDRD-equation); allograft loss defined by need/return to dialysis, Re-Transplantation, documented CAN, Death with a functioning graft were collected from the files.

Allograft dysfunction was defined as eGFR< 60mL/min/1.73 m². The estimated GFR (eGFR) was estimated using the abbreviated MDRD equation:

\[ eGFR \text{ (mL/min/1.73 m²)} = \exp (5.228 - 1.154) \times \ln (SCr)^{-0.203} \times \ln \text{ (age)}^{-0.299} \times 0.762 \times (if \ \text{female}) \times 1.212 (if \ \text{black}). \]

2.8 Data Processing & Analysis
All questionnaires were checked on daily basis for comprehensiveness and consistencies by the principal investigator.

Pre-coded data was entered into computer using stata version 20 for cleaning, categorizing continuous variables and eventual analyses.
Continuous data were summarized as mean ± standard deviation (SD), while discrete (categorical) data were recorded as percentage. Chi-square test was used to compare categorical variables. P-value of ≤0.05 was considered significant.

Univariate and multivariate logistic regression analysis was performed to determine predictors (exposure) of allograft dysfunction (outcome). The covariates with p-value of <0.05 were included in the model: (i) Recipient’s age, gender, primary renal disease, time on dialysis, BMI, blood pressure, rejection and change of eGFR (ii) Donor’s age, gender, BMI, relationship to patient/HLA (iii) Patient’s characteristics at 0, 3, 6 and 12 months; blood pressure, body mass index (BMI), proteinuria, and graft function estimated as chronic kidney disease stages.

2.9 Ethical Issues
The study ethical clearance was obtained from the Research and Publications Committee of Muhimbili University of Health and Allied Sciences (MUHAS). The permission to conduct the study at MNH was obtained from the ethical board of Muhimbili National Hospital. Waiver of consent was granted by the chairperson Research and Publications Committee of Muhimbili University of Health and Allied Sciences (MUHAS). All information from patient files were handled with maximum confidentiality.
CHAPTER THREE

3.0 RESULTS

3.1 Socio-demographics and clinical characteristics
A total of 182 files of recipients of renal transplant attending transplant clinic at MNH meeting the criteria of minimum three month post-transplant were reviewed for the purpose of this study. Demographic and clinical characteristics of the studied population are shown in Table 1a while those of the donors are shown in Table 1b. Out of 182 participants; 146 (80.2%) were male; mean age (SD) of recipients was 44.5(±12.5) years. Only four (2.2%) patients had previous history of transplant. Majority, 140(83.8%) had systolic blood pressure of <140mmHg at base line. First degree relatives were the main donors 130 (71%), males being 97 (53.3%) and the donor mean age (SD) was 35(±9) years.
Table 1a: Socio-demographic and clinical characteristics of the recipients (N=182)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n  ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (19.8)</td>
</tr>
<tr>
<td>Male</td>
<td>146 (80.2)</td>
</tr>
<tr>
<td><strong>Age Recipient</strong></td>
<td></td>
</tr>
<tr>
<td>12-30 years</td>
<td>26 (14.3)</td>
</tr>
<tr>
<td>31-45 years</td>
<td>65 (35.7)</td>
</tr>
<tr>
<td>45 – 60 years</td>
<td>70 (38.5)</td>
</tr>
<tr>
<td>Above 60 years</td>
<td>21 (11.5)</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>41 (22.5)</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>138 (75.8)</td>
</tr>
<tr>
<td>Widowed/divorced</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
</tr>
<tr>
<td>Primary Education</td>
<td>26 (14.3)</td>
</tr>
<tr>
<td>Secondary Education</td>
<td>73 (40.1)</td>
</tr>
<tr>
<td>Higher/post-secondary</td>
<td>83 (45.6)</td>
</tr>
<tr>
<td><strong>Recipient’s occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Civil servant</td>
<td>60 (33.0)</td>
</tr>
<tr>
<td>Businessman/self employed</td>
<td>87 (47.8)</td>
</tr>
<tr>
<td>Peasants</td>
<td>8 (4.4)</td>
</tr>
<tr>
<td>Others</td>
<td>27 (14.8)</td>
</tr>
<tr>
<td><strong>Relationship to donor</strong></td>
<td></td>
</tr>
<tr>
<td>First degree</td>
<td>130 (71.4)</td>
</tr>
<tr>
<td>Second degree</td>
<td>45 (24.7)</td>
</tr>
<tr>
<td>Third degree</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td><strong>Previous history of renal transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>No</td>
<td>178 (97.8)</td>
</tr>
<tr>
<td><strong>SBP at zero month (mmHg)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>140 (83.8)</td>
</tr>
<tr>
<td>≥140</td>
<td>27 (16.2)</td>
</tr>
</tbody>
</table>
Table 1b: Socio-demographic and clinical characteristics of the donors (N=182)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>97 (53.3)</td>
</tr>
<tr>
<td>Female</td>
<td>85 (46.7)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>22-30</td>
<td>61 (33.5)</td>
</tr>
<tr>
<td>31-45</td>
<td>95 (52.2)</td>
</tr>
<tr>
<td>46-60</td>
<td>25 (13.7)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>112 (61.5)</td>
</tr>
<tr>
<td>Overweight</td>
<td>64 (35.2)</td>
</tr>
<tr>
<td>Obese</td>
<td>6 (3.3)</td>
</tr>
</tbody>
</table>

3.2 The native kidney disease and comorbidities in renal recipients

Figure 1 shows the main native kidney diseases and comorbidities among renal transplant recipients. Hypertension was the most common 85(47%) cause of native kidney disease followed by glomerulonephritis 40(23%). Diabetes was documented as primary comorbidities in 22(12.1%) patients and those with both diabetes and hypertension were reported to be 21(11.5%) patients. Other contributors are as shown in Figure 1 below.
3.3 Prevalence of allograft dysfunction at 0, 3, 6 and 12 months of follow-up
The cumulative prevalence of allograft dysfunction was 2.2 % at month 0, 4.9% at month 3, 28.6% at month 6 and 37.4 % at month 12 post transplantation. Figure 2.
3.4 Association between allograft function and patients’ characteristics

Proteinuria was found to have significant association with graft dysfunction at all-time points during the 1\textsuperscript{st} year post-transplant. The proportion of those with proteinuria and dysfunction being >50\% and p-value ranging from 0.03 to <0.01 as shown in table below on Patients’ characteristics and allograft dysfunction among kidney recipients.

Systolic blood pressure (SBP) and BMI showed significant association of p-value <0.01 and 0.04 respectively at one year post-transplant with those with elevated SBP>140mmHg about two third having dysfunction.

History of episode of rejection, which was confirmed by biopsy, showed to have association with dysfunction. We found more than three quarter of those with documented biopsy report, episode of rejection was associated with graft dysfunction at month six and twelve with, p-value <0.01. These are shown on Table 2a-b.
Table 2a: Patients’ characteristics and allograft dysfunction among kidney recipients at different time points (n=182)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with allograft dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>n=171(%)</td>
</tr>
<tr>
<td></td>
<td>22(52.38)</td>
</tr>
<tr>
<td>NO</td>
<td>42(32.56)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.03</td>
</tr>
<tr>
<td>Recipient’s BMI (Kg/m^2)</td>
<td>N=182</td>
</tr>
<tr>
<td>Normal</td>
<td>3(1.8)</td>
</tr>
<tr>
<td>Overweight</td>
<td>0(0)</td>
</tr>
<tr>
<td>Obese</td>
<td>1(25)</td>
</tr>
<tr>
<td>Severely obese</td>
<td>0</td>
</tr>
<tr>
<td>p - value</td>
<td>0.1</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>N=167</td>
</tr>
<tr>
<td>&lt;140</td>
<td>2(1.43)</td>
</tr>
<tr>
<td>≥140</td>
<td>2(7.41)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.1</td>
</tr>
<tr>
<td>Rejection Episodes</td>
<td>N=182</td>
</tr>
<tr>
<td>Treated with anti-rejection therapy</td>
<td>1(9.1)</td>
</tr>
<tr>
<td>Not treated with anti-rejection therapy</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>unknown</td>
<td>3(1.8)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.3</td>
</tr>
<tr>
<td>Dialysis Duration</td>
<td>N=182</td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>1(2.27)</td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>3(3.03)</td>
</tr>
<tr>
<td>≤ 2 years</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>p - value</td>
<td>1</td>
</tr>
<tr>
<td>Recipient Age (years)</td>
<td>N=182</td>
</tr>
<tr>
<td>≤ 30</td>
<td>1(3.9)</td>
</tr>
<tr>
<td>31-45</td>
<td>2(3.1)</td>
</tr>
<tr>
<td>46-60</td>
<td>1(1.4)</td>
</tr>
<tr>
<td>60+</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.8</td>
</tr>
</tbody>
</table>

NOTE: *171
Among donor factors that were assessed as predictors of dysfunction only BMI showed to have impact on graft dysfunction with higher BMI to have association with dysfunction p-value 0.04 and 0.01 at 6 and 12 month respectively.

Table 2b: Donors’ characteristics and allograft dysfunction among kidney recipients at times post-transplant. N=182.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recipients with graft dysfunction at different time points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
</tr>
<tr>
<td><strong>Donor Age (years)</strong></td>
<td>Number (%)</td>
</tr>
<tr>
<td>≤30</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>31-45</td>
<td>4(4.21)</td>
</tr>
<tr>
<td>46-60</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>60+</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Donor Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2(2.35)</td>
</tr>
<tr>
<td>Male</td>
<td>2(2.06)</td>
</tr>
<tr>
<td>p - value</td>
<td>1</td>
</tr>
<tr>
<td><strong>Donor BMI(Kg/m²)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1(0.89)</td>
</tr>
<tr>
<td>Overweight</td>
<td>3(4.69)</td>
</tr>
<tr>
<td>Obese</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>p - value</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>HLA Matching</strong></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>1(6.67)</td>
</tr>
<tr>
<td>One</td>
<td>1(2.04)</td>
</tr>
<tr>
<td>Two</td>
<td>1(2.08)</td>
</tr>
<tr>
<td>Three</td>
<td>0(0.00)</td>
</tr>
<tr>
<td>Others</td>
<td>1(14.29)</td>
</tr>
<tr>
<td>p – value</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*(n=171); **(n=152)
The mean eGFR at 0, 3, 6, and 12 months post renal transplantation was 82±14, 78±18.51, 73±19 and 71±23.28 mL/min/1.73 m² respectively. The table below also shows percentages of different stages at study points with overall deterioration of stages (Table 3).

**Table 3: Recipients’ post-transplant CKD_T stage and the mean change of eGFR N=182**

<table>
<thead>
<tr>
<th>CKD STAGE</th>
<th>TIME (MONTH) SINCE TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
</tr>
<tr>
<td>stage I</td>
<td>62; 34%</td>
</tr>
<tr>
<td>stage II</td>
<td>116; 63.8%</td>
</tr>
<tr>
<td>stage ≥ III</td>
<td>4; 2.2%</td>
</tr>
<tr>
<td>Mean(±SD)eGFR (ml/min/1.73m²)</td>
<td>82±14</td>
</tr>
</tbody>
</table>

Further logistic regression analysis by univariate was done and elevated donor BMI, systolic blood pressure of ≥140mmHg, drop change of GFR from baseline, presence of proteinuria at twelve month showed to have negative impact on graft. On multivariate analysis, significant predictors of allograft dysfunction were; eGFR drop from baseline (AOR (95% CI) 3.98(1.11-14.36), recipient SBP 1.15(1.08-1.23) and proteinuria at 12 months 2.71(1.04-7.06) Table 4.
Table 4: Predictors of allograft dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR(95%CI)</th>
<th>p-value</th>
<th>OR(95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=30</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-45</td>
<td>1.63(0.62-4.29)</td>
<td>0.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-60</td>
<td>1.08(0.41-2.82)</td>
<td>0.866</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61+</td>
<td>0.94(0.24-3.62)</td>
<td>0.934</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donor BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>2.70(1.44-5.38)</td>
<td><strong>0.002</strong></td>
<td>0.26(0.06-1.16)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Recipient BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>0.60(0.25-1.42)</td>
<td>0.247</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=140</td>
<td>2.87(1.20-6.87)</td>
<td><strong>0.018</strong></td>
<td>3.98(1.11-14.36)</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td><strong>Dialysis duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6months</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One year</td>
<td>0.85(0.39-1.86)</td>
<td>0.329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=two years</td>
<td>0.68(0.25-1.83)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donor age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=30</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-45</td>
<td>1.4(0.69-2.91)</td>
<td>0.161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-60</td>
<td>2.0(0.75-5.63)</td>
<td>0.329</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR Drop date</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>1.05(1.02-1.09)</td>
<td><strong>0.001</strong></td>
<td>1.01(0.96-1.07)</td>
<td>0.959</td>
</tr>
<tr>
<td>0.6</td>
<td>1.14(1.09-1.20)</td>
<td><strong>0.001</strong></td>
<td>1.02(0.94-1.10)</td>
<td>0.447</td>
</tr>
<tr>
<td>0.12</td>
<td>1.16(1.11-1.23)</td>
<td><strong>0.001</strong></td>
<td>1.15(1.08-1.23)</td>
<td><strong>0.00</strong></td>
</tr>
<tr>
<td><strong>Proteinuria at 0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2.05(0.99-4.23)</td>
<td>0.052</td>
<td>1.2(0.25-5.37)</td>
<td>0.850</td>
</tr>
<tr>
<td>negative</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria at 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2.44(1.04-5.74)</td>
<td>0.040</td>
<td>1.99(0.77-5.16)</td>
<td>0.157</td>
</tr>
<tr>
<td>negative</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria at 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2.72(0.99-7.45)</td>
<td>0.052</td>
<td>0.2(0.02-2.72)</td>
<td>0.255</td>
</tr>
<tr>
<td>negative</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria at 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3.42(1.39-8.42)</td>
<td><strong>0.007</strong></td>
<td>11(1.1-11.06)</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td>negative</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.5 Outcome of allograft dysfunction

Table 5: Shows outcome in the first one year of renal transplant, whereby 59.9 % (109) patients had stable graft, 30.2% had graft dysfunction that was less than ESRD, while 3.8 % (7) had ESRD and 6.0 % (11) had death with functioning graft as elaborated below.

Table 5: Recipient outcome in the first one year of renal transplant N=182

<table>
<thead>
<tr>
<th>Outcome of allograft dysfunction</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD not on dialysis</td>
<td>3</td>
<td>1.6</td>
</tr>
<tr>
<td>Return to dialysis</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Work up for repeat of transplant</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Repeated transplant</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death from ESRD</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Stable graft function</strong></td>
<td>109</td>
<td>59.9</td>
</tr>
<tr>
<td>Dysfunction not amounting to ESRD</td>
<td>55</td>
<td>30.2</td>
</tr>
<tr>
<td>Death with functioning kidney</td>
<td>11</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>182</td>
<td>100</td>
</tr>
</tbody>
</table>

3.6 Causes of death with functioning graft.

The cause of death in majority of patients (64%) was related to cardiovascular cause followed by infection (18%), cancer (9%) and in 9% the cause of death could not be ascertained. The distribution of causes of death with the functioning graft are shown in Figure 3 below.
In the course of this study, 26 patients (14.3%) developed NODAT with 29 patients documented to have checked blood sugar at least once in the first year after return from transplant center.

Referring to WHO anemia criteria; 78(42.8%), 61(33.5%), 40(21.9%) and 46(27%) had anemia at zero month, three months, six months and one year post transplant respectively.

Common immunosuppressant used was prednisolone in all patients, followed by tacrolimus, cyclosporine/MMF in that order.
CHAPTER FOUR

4.0 DISCUSSION

In this study, a total of 182 post renal transplant patients were evaluated for prevalence, predictors and outcome of allograft dysfunction. The mean age of the recipients was 44.5±12.5 years and 35±9 years for the donors. Almost half of the study participants were hypertensive, and had undergone haemodialysis for at least a year, with only 4 patients documented to have undergone dialysis for ≤ 6month. Almost three quarters of the donors were the patients’ first degree relatives. Elevated systolic blood pressure, proteinuria and rate of decline of renal function were independent predictors of renal allograft dysfunction.

The prevalence of allograft dysfunction (in this study defined as GFR<60ml/min/1.73m²) was found to be increasing with follow up duration post-transplant. Proteinuria and change of eGFR were found to be associated with dysfunction. On multivariate analysis; elevated SBP proteinuria and change in eGFR emerged as independent predictors of allograft dysfunction.

4.1 Demographic characteristics for recipient and donors

Age at transplant

More than four fifths of the participants in this study were under the age of 60 years. Which is comparable to the study done by Maro et al in which 92.3% were less than 55years at the time of transplant⁸. Our findings differ from other studies conducted in America and Europe at different transplant centers whereby median patient age at time of diagnosis of ESRD in the United Kingdom was 64.9 years⁷⁷, this difference could be due to the fact that the age limit for kidney recipients in Tanzania is 65 years unlike most of the developed countries where recipients older than 65 years may receive an allograft/kidney transplant. Studies have shown that older age is not a contraindication for renal transplant as it doesn’t affect graft survival but has been associated with death with functioning graft due to other factors including cardiovascular disease related deaths²⁷.
Contrary to recipient age, donor age seem not to have effect on graft survival. This study had three donors who were above 55 years and one being above 60 years. The mean age of donor was 35±9 years which is comparable to another study done in Canada where the mean donor age was 33.9±15 years. A limited number of donors above age 55 years in this study could have attenuated the association between donor age and graft dysfunction. Studies have shown advanced age cause changes on the renal anatomy including glomerulosclerosis, interstitial fibrosis and thickening of the arterioles. Another study showed advanced donor age was associated with delayed graft function which had effect on graft function post-transplant.

**Donor gender**

Over half of the donors in this study were male. Gender showed no association with the graft function at one year, similar to a study by Surazee in which gender showed no effect on GFR at < 5yrs post-transplant but a borderline effect if was > 5yrs. In contrary, another study showed a decrease in graft survival from female donor with postulation that women have smaller kidneys and hence have relatively fewer number of nephrons than men.

**BMI**

In this study, recipient BMI was not associated with graft dysfunction at month 0, 3 and 6 but was significantly associated with graft dysfunction at month 12 post transplantation. At the beginning of transplant most of patients had been chronically ill and underwent hemodialysis for an extended period which could have impacted on body weight making them fall on a normal range BMI and at one year the that the of BMI seemed evident. A study by Raiss Jalali et al also showed that it mostly the BMI before transplant that effect on allograft function with those overweight facing impact on allograft.

Elevated BMI particularly obesity in non-transplant patients has been associated with hypertension, hyperlipidemia, type II diabetes, proteinuria and glomerulopathy. Hence it is possible that renal transplant recipients with an elevated BMI may have worse long term graft survival.
Duration of dialysis prior to transplant

This study found no association between dialysis duration and allograft dysfunction while other study showed the effect of duration of dialysis on allograft function and found the association between an increased duration of dialysis before transplantation and increased odds of acute rejection by six months supporting the concept of an immunologic effect of dialysis\textsuperscript{82}. In this study, no data showed preemptive dialysis while there were 44(24.2\%) patients with ≤6 month duration of dialysis, over half 101(56\%) had had dialysis for one year while 7(3.8\%) had undergone dialysis for more than two years. In other study on influence of duration of dialysis and outcome showed more than half had undergone HD for more than two years and duration of dialysis had effect on graft\textsuperscript{83}. Compared to outcomes following preemptive transplants, waiting times of 0 to 6 months, 6 to 12 months, 12 to 24 months, and over 24 months conferred a 17, 37, 55, and 68\% increase in risk for death-censored graft loss after transplantation, respectively\textsuperscript{84}. In our study, such a deeper analysis was limited due to small number (only four) of shorter dialysis duration and 7(3.8\%) longer to run regression.

4.2 Prevalence of allograft dysfunction

With the definition of allograft dysfunction in this study as eGFR ≥60 ml/min/1.73m\(^2\), the cumulative prevalence of allograft dysfunction in our study rose from 2.2 \% immediately post transplantation to 37.4 \% at one year post-transplant. Our findings are different from a study done by Siddiqi N at el where the overall prevalence of renal dysfunction at 1 year post-transplant (SCr > 1.5 mg/dL) was 54.5\% in 1988 and 42.3\% in a repeat study in the year 1999. This could probably be explained by different study times as less usage of cyclosporine and in preference of mycophenolate mofetil and tacrolimus in 1990s could have led to a reduction in the incidence of acute allograft rejection during the first year after transplantation. In our study, 80\% of our patients were on Mycophenolete mofetil (MMF), Tacrolimus and prednisolone combination. Tacrolimus has shown to have no effect on graft loss or mortality.
rates at 1 year and the incidence of acute rejection at 1 year was lower among patients treated with tacrolimus, compared with Cyclosporine (CsA).

4.3 Predictors of allograft dysfunction

Blood pressure
In this study 46.7% recipients had hypertension as the disease which was attributed to native kidney damage. This high incidence of hypertension was also observed in previous study done in Tanzania by Kisanga et al on quality of life where HTN led by 58.8% (unpublished). The American Society of Transplantation (an older guideline) recommends target BP levels of <140/90 mmHg to renal recipient\(^85\). We found that elevated systolic blood pressure was independently associated with graft dysfunction. This was also seen in another study on association on recipient blood pressure and graft failure, that showed that increased blood pressure was an independent risk factor for poor graft function\(^86\) whereas another study has shown that both systolic and diastolic hypertension were independent risk factors for graft and patient loss in kidney transplant recipient\(^87\).

In this study, almost two thirds (63.6%) of patients who died with a functioning kidney allograft had cardiovascular causes as the main cause for their death. This finding was comparable to that from a study done by Pieter who reported cardiovascular diseases as the leading cause of mortality in death with functioning graft\(^88\). Immunosuppressants may lead to progressive hypertension following transplant through various mechanisms including endothelin-induced vasoconstriction, nullification of nitric oxide–induced vasodilatation, and sodium retention which could explain challenge in controlling hypertension and its associated cardiovascular complications during post transplantation follow up\(^89\).

Proteinuria
Transient proteinuria is common and is often associated with episodes of acute allograft rejection and may not affect allograft or patient survival independent of its underlying cause. Persistent proteinuria is usually defined as protein excretion of .0.5 to 1.0 g/24 h for at least 3
to 6 month\cite{90}. In our study incidence of proteinuria at month zero post transplantation was 42% while at 12 months was 26%. This was comparable to another study that showed that the incidence of proteinuria in the post kidney transplantation patients ranged between 10% and 25\%\cite{91}. Proteinuria from the native kidneys normally resolves within the first 1 to 10 weeks post transplantation\cite{92}. This could explain the decline in incidence of proteinuria from month 0 to 12 months post-transplantation that we observed in this study.

It also known in the absence of recurrent or de novo glomerulonephritis allograft nephropathy is the ultimate reason for proteinuria and one of the most important causes of proteinuria is hypertension, but also more kidney/recipient size mismatch, quality of the graft and activation of the intrarenal renin angiotensin system have also been recognized to have influence on proteinuria\cite{93}.

In our study presence of proteinuria was significantly associated with allograft dysfunction at all study follow up time points. This was also observed in another study which assessed the degree of proteinuria being associated with dysfunction\cite{94}. It is believed that protein-loaded epithelial cells express more major histocompatibility complex (MHC-2) antigens, exposing them to immune reactions that may lead to progressive allograft dysfunction\cite{95}.

**Change of estimated GFR**

The mean eGFR at 12 month was 71±23.28 mL/min/1.73 m\(^2\) with rate of decline of eGFR at -11±9.28 mL/min/1.73m\(^2\) per year. This decline of GFR was associated with graft dysfunction in our study. This was similar to the PORT study by Kasiske et al that also showed a negative eGFR slope between 3 and 12 months was associated with graft failure\cite{96}. This finding was however different from the multicenter study done by Roberto M et al\cite{101} which had lower eGFR at 12 month but with slope of -1.12±0.05 and the decline was not associated with poor graft function. The difference seen in our study could be attributed to including participants with at least duration of 3 month post transplantation\cite{97}. Studies have concluded that regular
monitoring of renal function allow identification of those patients at highest risk of graft failure and provide room for improving outcomes\textsuperscript{98,99}.

**HLA match**

All transplant recipients and their respective donors undergo tissue typing to determine the HLA. Six (6) HLA antigens are determined. Mismatches between donor and recipient HLA increase the risk of rejection\textsuperscript{100}. In our study almost three quarters (71.4\%) of the donors were first degree relatives and only very few (3.9\%) were third degree relatives. Almost half (48.4\%) had a more than haplomatch, and less than one tenths (8.2\%) had a zero HLA match while around one fifths (19.7\%) had missing data on HLA matching. With these findings in our study HLA seemed to have no effect on graft dysfunction as majority had good HLA matching and with first degree relationship. This could as well be explained by availability of immunosuppressant which can allow spouse with HLA mismatch to be donor as observed in this study. Our study is in keeping with the study by Surazee Prommool et al which showed HLA matching was more impactful on allograft function during early allograft rejection but showed no correlation on allograft dysfunction when analyzed by univariate and multivariate with HLA-A,B mismatch\textsuperscript{82}.

**Cause of ESRD in native kidneys**

There was no significant association between allograft dysfunction and primary renal disease in our study. In contrary to a study by Courtney et al\textsuperscript{101} which showed that underlying cause of ESRD may affect renal transplantation survival rate in long-term. It should be noted that our study duration was limited to one year post-transplant while recurrence of native disease takes time to develop and also most of prospective renal recipients are referred for transplant evaluation with already shrunken non-functional kidneys without any known underlying disease. Furthermore, diagnosing the underlying cause of kidney disease requires a kidney biopsy that was still not widely practiced at our center during our study time.
**Episode of rejection**

In our study few patients had confirmed diagnosis of rejection by biopsy, these biopsy documented episodes of rejection showed the correlation with the allograft dysfunction. This finding was also seen in a study by Mojgan and colleagues whereby confirmed episodes of rejection had a negative impact on long-term renal allograft survival\textsuperscript{102}.

Although subclinical rejection may be seeming only on biopsy of the organ and, in the absence of renal dysfunction the increase in serum creatinine may point toward graft rejection\textsuperscript{103} but also other study has shown transit proteinuria might indicate acute rejection when in nephrotic range\textsuperscript{104}. With these findings including high incidence of proteinuria which was noted at baseline which could not of certain concluded to be a result of native kidneys/reflecting perioperative ischemic damage and 152 patients had raise in creatinine but wasn’t investigated by biopsy to nullify the rejection thus interpretation of this finding in our study should be done with care.

**NODAT**

New onset diabetes after transplant (NODAT) is believed to be caused primarily by glucocorticoids, CsA, and tacrolimus. In our study 26 patients (14.3\%) developed NODAT .In other large studies, the incidences of post-transplant diabetes mellitus were (3.6\%) - (11.7\%)\textsuperscript{105}. This incidence in our study is higher and could be explained by poor compliance to follow the recommendation to regular check drug levels mainly due to high cost in private hospitals and unavailability to our hospital. Drug such as tacrolimus when in high serum level has be associated with NODAT.
CHAPTER FIVE

5.0 STRENGTHS AND LIMITATIONS

5.1 Strength
The study was conducted in a well-organized major post-transplant clinic in Tanzania comprises a large proportion of post-transplant patients.

5.2 Limitations
Lack of complete documentation in files and missing laboratory results in the geeva system.
CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion.
The burden of allograft dysfunction in the 1st year of kidney transplant is high among patients attending post-transplant clinic at MNH. Independent predictors for allograft dysfunction include raised systolic blood pressure, proteinuria and rate of eGFR drop.

6.2 Recommendations
With this knowledge, we could try reduce the prevalence of graft dysfunction by close monitoring of high risk or combination of high risk factors in recipients. Aggressive blood pressure control should be emphasized and monitoring of proteinuria both qualitatively and quantitatively is crucial as well as use of ACEi or ARB has studies have shown some beneficial on being renal protective.
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Appendix 1: Informed Consent (English Version)

CONSENT FORM TO PARTICIPATE IN THE STUDY.

TITLE: PREDICTORS AND OUTCOME OF ALLOGRAFT DYSFUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT MUHIMBILI NATIONAL HOSPITAL

Hello! My name is Dr Batanyita Julieth, a Resident in the department of Internal Medicine. I would like to conduct a study mentioned above for my dissertation.

The aim of the study is to determine predictors and outcome of allograft dysfunction among kidney transplant recipients attending renal transplant clinic at MNH.

By determining baseline modifiable factors related to post - transplant allograft dysfunction, clinicians may intervene appropriately and timely and consequently optimize post-transplant graft function.

Patients who meet the inclusion criteria will be recruited into the study using their data in files.

Using a structured questionnaire, which will include their social demographic characteristics and clinical examination and undergo Laboratory investigations including SCr, electrolytes, Hb level, lipid profile and virology.
Data from transplant center such as donor age, relationship, HLA results, and initial serum creatinine post-transplant will be obtained.

We don’t suppose any harm to happen to you as a result of joining this study and information obtained will be confidential.

No payment is demanded as a fee to participate in the study.

You have a right to agree or disagree to participate in this study.

If you choose to not participate or if you decide to stop participate in the study, the hospital will continue to provide all the services, which you would normally get accordingly.

For any questions about this study you are free to contact the Principal Investigator, Dr. Batanyita Julieth 0788647171 OR Dr. P. Ruggajo (Tel: 0688 836235/ 0755 738165) Department of Internal Medicine, MUHAS OR PROF. Eden Maro 0715 260 153 Department of Internal Medicine, MUHAS.

If you have any questions/concerns about your rights as participant you may contact Prof. Said. Aboud, Chairman of MUHAS Research and Publications Committee, P. O. BOX 65001, Dar - es - Salaam. Tel 2150302-6

I………………………………………………. have read/been told of the contents of this form and understood its meaning. I agree to participate in this study.

Signature………………….. (Participant) Date…………………

Signature………………….. (Researcher) Date…………………
Appendix 2: Questionnaire

TITLE: PREDICTORS AND OUTCOME OF ALLOGRAFT DYSFUNCTION AMONG KIDNEY TRANSPLANT RECIPIENTS AT MUHIMBILI NATIONAL HOSPITAL

1. Study Number

2. Hospital Number _______________________

3. Name of recipient _______________________

4. Date of transplant <dd/mm/yyyy>

5. Transplant center ___________

6. Patient status ___________
   1. Alive      2. Dead

7. If alive
   1. On dialysis      2. Not on dialysis

8. If dead
   Cause of death ____________________________________________
   1. ESRD      2. Cardiovascular      3. Infection      4. Others
9. Date of interview -------------------

SOCIO-DEMOGRAPHIC DATA

10. Age of recipient (complete years): ....................

11. Sex of recipient: ....................
    1. Male    2. Female

12. Address: ______________________________
    1. Dar es Salaam       2. Abroad

13. If Abroad (mention): ........

14. Phone contacts:.............

15. Marital status: ............

16. Educational level: .............

17. Occupation: ....................
18. If Others (mention): ..................

19. Relationship to donor: ..............
   1. First degree  2. Second degree  3. A friend/husband/wife

20. Donor age: .....................

21. Donor sex: ......................
   1. Male  2. Female

22. If female number of pregnancy carry term.............
   1. None  2. Single  3. Multiple

23. Donor BMI: .................
   1. 0-18.5 Underweight  2. 19-24 Normal  3. 25-30 Overweight
   4. 31-35 Obese  5. 36-40 Severely Obese

24. Number of HLA haplotype matches: ..............
   6. Data missing)

25. Health insurance: ..............
   1. Yes  2. No

CLINICAL BACKGROUND

Recipient Vital signs:
26. Blood pressure in mmHg
At 0 month
At 3 month
At 6 month
At 1 year post transplant

27. BMI (kg/sqm)
At 0 month
At 3 month
At 6 month
At 1 year post transplant

28. FBG/RBG
1. Done 2. Not done
If done
At 0 month
At 3 month
At 6 month
At 1 year post transplant
1. Normal 2. Not normal

29. NODAT
1. Yes 2. NO

30. Hb A1c (if indicated)
At 0 month
At 3 month
At 6 month
At 1 year post transplant

31. Past history of established kidney disease:
   1. Yes    2. No    3. Don't know

32. The cause of prior kidney disease:
   1. Diabetes mellitus
   2. Hypertension
   3. Glomerulonephritis
   4. Cystic kidney disease
   5. Interstitial disease
   6. Unknown or other causes, or data missing)

TICK APPLICABLE
33. Family history of kidney diseases
   1. Yes    2. No    3. Don't know   (risk of recurrence)

34. Type of dialysis before transplant
   1. None    2. Hemodialysis    3. Peritoneal dialysis

35. Duration of dialysis ..............  PREDICTOR
   1. 6 month    2. 1 year    3. 2 years    4. > 2 years

36. Have you ever been transfused prior transplant?
   1. Yes    2. No
37. If yes
   1. Once  2. Multiple

38. History of previous renal transplant
   1. Yes  2. No

39. Immunosuppressant drug on
   1. Calcineurin inhibitors (e.g., cyclosporine and tacrolimus)

   2. Antiproliferative agents (e.g., azathioprine and mycophenolate)

   3. Corticosteroids

40. Have you ever tested for drug levels post-transplant
   1. Yes  2. No

41. If yes, __________________________________________________________
   1. Normal range  2. Abnormal range

42. Did patient have any rejection episodes during the follow-up period?

   1. Yes, at least one episode treated with anti-rejection agent
   2. Yes, none treated with additional anti-rejection agent
   3. No
   4. Unknown
43. Was biopsy done to confirm rejection?
1. Biopsy not done
2. Yes, rejection confirmed
3. Yes, rejection not confirmed
4. Unknown

44. Type of Rejection
1. Acute
2. Chronic

45. History of BT
1. None  2. Single  3. Multiple

LABORATORY PARAMETERS

46. Blood grouping and cross matching
Donor _______________ Patient _______________

<table>
<thead>
<tr>
<th></th>
<th>At 0mnth</th>
<th>3mnth</th>
<th>6mnth</th>
<th>12mnth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>_________</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Protein/albumin</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Nitrates</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>

47. Urine analysis: - microscopic PREDICTOR

<table>
<thead>
<tr>
<th></th>
<th>At 0mnth</th>
<th>3mnth</th>
<th>6mnth</th>
<th>12mnth</th>
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<tr>
<td>Blood</td>
<td>_________</td>
<td>_______</td>
<td>_______</td>
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<tr>
<td>Protein/albumin</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
<tr>
<td>Nitrates</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
<td>_______</td>
</tr>
</tbody>
</table>
48. 24 hours urine protein _
   1. Done
   2. Not done

Results:
At0month _______________________________________________
At3month _______________________________________________
At6month _______________________________________________
At1yearposttransplant _________________________________________
(1. - 2. +1 3. +2 4. +3)

49. Serum creatinine normal?

Estimated GFR
Stage
At0month _______________________________________________
At3month _______________________________________________
At6month _______________________________________________
At1yearposttransplant _________________________________________


50. Lipid profile normal?
   1. Yes
   2. No

51. HIV status _____________________________________________
   1. Positive
   2. Negative

52. Hepatitis    BsAg __________________________________________
1. Positive 2. Negative

53. Hepatitis C ____________________________________________
   1. Positive 2. Negative

54. CMV IgG ________________________________________________
   1. Yes 2. No)

56. CMV IgM ________________________________________________
   1. Yes 2. No)

56. FBP
   Wbc
   At0month ________________________________________________
   At3month ________________________________________________
   At6month ________________________________________________
   At1yearposttransplant ______________________________________

HB g/dl
   At0month ________________________________________________
   At3month ________________________________________________
   At6month ________________________________________________
   At1yearposttransplant ______________________________________

   1. Normal 2. Low 3. High)

RADIOLOGICAL
62. Death due to other cause with functioning kidney cause?
   1. Infection
   2. Cancer
   3. Cardiovascular
   4. Unknown cause)