Review of Adult Kidney Transplant Recipients at Charlotte Maxeke Johannesburg Academic Hospital Between January 2012 to January 2020

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Declaration

I, Kyle David Schnaar, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature: 

Date: 02 April 2025

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Disclosure

None

Abstract

Background: Kidney transplantation is a lifeline for individuals with end-stage kidney failure, offering quality of life, financial and survival benefit over chronic dialysis. Kidney transplantation is complex and dependent on multiple donor and recipient factors. Ensuring longevity of future allografts requires understanding of limitations to previous allografts.

Objectives: Review the most common outcomes encountered in KTR at a state hospital in Gauteng, South Africa

Methodology: This was a single centre retrospective record review of all first-time adult renal transplant recipients from 01 January 2012 to 31st January 2020. Data collected included demographic and clinical parameters. Complications post-transplantation were noted. Outcome end points were recipient death and graft loss (defined by a need to return to dialysis).

Results: One-hundred and sixty-seven (167) patients over 18 years old received renal transplants at our facility between 1 January 2012 and 31 January 2020, 140 were included, of which 94 (67.1%) were male and 46 (32.9%) were female. The mean (SD) age at transplant was 41.9 years (10.5 years). Hypertension was noted as the principal aetiology for renal failure in 81 (57.9%) patients. One-hundred and twenty-eight (128, 91.4%) received a cadaveric kidney transplant and 12 (8.6%) received a kidney from a living donor. Median time to discharge was 18 days (IQR 11-32 days). 63 (45.0%) patients experienced delayed graft function, of which 45 (71%) received dialysis support. 49 (35%) patients experienced graft loss with a median time to loss of 30 months (IQR 6-52 months). Anaemia and delayed graft function were significant risk factors for graft loss, ($p<0.001$). Antibody-mediated

rejection, T-cell mediated rejection and BK nephropathy all proved significant risk factors for graft loss ($p<0.001$, $p=0.002$, and $p=0.003$ respectively). Other complications included 39 (27.9%) KTR developed post-transplant diabetes, and 8 malignancies occurred in 7 (5.0%) KTR. Thirty-nine (27.9%) patients demised throughout the study period the primary cause of death was sepsis with 21 (53.9%) deaths.

Conclusion: Sepsis was a major cause of death and graft loss. Fifty-five percent (55%) of recipients had a functioning graft at 5 years. Further studies are required to determine factors influencing long term graft outcomes in our population.

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Nomenclature

ABMR	Antibody (Humoral) Mediated Rejection
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DSA	Donor-Specific Antigens
DGF	Delayed Graft Function
EGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
HIV +	Human Immunodeficiency Virus Positive
HIV -	Human Immunodeficiency Virus Negative
IQR	Inter-Quartile Range
KTR	Kidney Transplant Recipient(s)
PTDM	Post-Transplant Diabetes Mellitus
RRT	Renal Replacement Therapy(ies)
TCMR	T-Cell Mediated Rejection
UTI	Urinary Tract Infection(s)

Chapter 1: Protocol with extended literature review

Extended Literature Review and rationale

The burden of chronic disease in South Africa (encompassing both communicable and non-communicable) has increased over the previous decades, partly due to an increase in the aging population.[1,2] End-stage kidney disease (ESKD) is one such condition that has been on the rise.[3] This ever-expanding cohort of individuals with ESKD is accompanied by an increased demand for renal replacement therapies (RRT); a demand, which unfortunately outweighs available resources.[3-5]

Internationally the standard for RRT in ESKD is kidney transplantation, as this offers a multitude of benefits to the kidney transplant recipients (KTR) as well as the financial cost bearer.[6,7] Thus, it is essential to ensure the longevity of existing KTR allografts to improve the quality of life for the KTR, while reducing the cost of care to the KTR or state. KTR are therefore monitored under specialist care post-renal transplantation to ensure the prevention of allograft failure, to contribute to the development of effective management regimens for the recipient and future recipients, and promote efficient use of limited resources.[4,8]

Despite South Africa being one of the most active proponents of renal transplantation on the African continent, our success rates are still outmatched by those of more developed nations.[5,9,10] Reasons for this discrepancy include primary reliance on deceased donors as well as high cost of patient care pre- and post-transplantation (e.g. access to specialists, medications, dialysis etc.).[5,9,11]

Post-transplant adverse outcomes include (but are not limited to) hospitalisation, unexpected financial expenses, dysfunction or failure of the allograft, and death.[8] These put further strain on an already overburdened healthcare system. Thus, it is

the responsibility of both the KTR and healthcare professionals to detect problems early and intervene timeously.

Graft Loss as a Consequence of Death

Cardiovascular disease

Graft loss is multifactorial and death of a KTR is an important cause of graft loss.[12] The first three months post-transplantation are associated with the highest incidence of mortality, with the deaths being attributable predominantly to cardiovascular disease (CVD) and infections.[13] After one-year post-transplant, deaths due to CVD and malignancy have an increase in incidence.[13] Over the past few decades KTR survival has improved, with reductions in mortality associated with CVD, sepsis, and malignancy.[13] International data suggests that despite an overall reduction in CVD-associated deaths in KTR, CVD remains an important risk factor.[13-15] In contrast, South African data shows that sepsis is the main contributor to KTR mortality, followed by CVD and malignancy.[16] It is imperative that rates of sepsis be considered in the South African context of limited resources and considerable prevalence of communicable diseases.[16]

Anaemia

Incidence of cardiovascular events and cardiovascular related deaths post-transplantation are increased in KTR with anaemia.[17] Anaemia is a common complication post-transplantation that is multifactorial in aetiology, with implications for graft loss and mortality independent of other risk factors.[18-20] The incidence and aetiology of anaemia may vary dependent on the timing of onset, whether early post-transplantation: within 6 months of transplant or late post-transplantation: beyond 6 months.[20] The impact of anaemia on graft loss and overall mortality may be affected

by the timing of onset (early vs late) as well as the severity of the anaemia, with early onset severe anaemia (defined as a haemoglobin <11g/dL) having increased incidence of graft loss and mortality.[17,19,20]

Sepsis

Infections are an important cause of death in KTR who are at particular risk due to the need for immune suppressive therapy.[8,13] Infections are not limited to post-transplant acquisition but may be present pre-transplantation, from either the donor or recipient.[8,22,23] To mitigate the risk of post-transplant infection, pre-transplant workup includes screening to prevent a donor-recipient "mismatch" (donor-positive to a recipient-negative) as well as to identify potential KTR who require vaccination pre-transplantation.[22] Work-up is inclusive of: HIV, hepatitis B, hepatitis C, Epstein-Barr virus, syphilis, tuberculosis, cytomegalovirus, and varicella zoster.[22] Donor BK virus pre-transplant screening may also have utility in predicting post-transplant recipient outcomes.[23] Whilst viral infection may not necessarily exclude a donor or recipient, its presence may warrant specific therapy and potentially affect outcomes.[22]

Post-transplant infections may be categorized:

- Early-onset: occurring within 30 days post-transplant
- Peak immunosuppression: beyond the first month but within the first year
- Late-onset: occurring beyond 1-year post-transplantation[24]

Dependent on the period post-transplantation that the KTR develops sepsis, the likely site of infection and organism may differ.[8,24] **Table 1**, adapted from Agrawal et al[24] 2022, describes the correlation between common infections and time periods elapsed post-transplant.

Table A: Sepsis associated with time post renal transplantation[24]

Early-onset	Peak Immunosuppression	Late-Onset
Donor-Derived Infections • HCV, HBV, T.Cruzi, LCMV, Bacteraemia, endemic mycosis	On Prophylaxis • HCV • Polyomaviruses (BK virus) • Cryptococcus neoformans • MTB • Strongyloides • Leishmania • PTLD	Opportunistic infections • CMV • JC/PML • PTLD/EBV • Nocardia
Recipient-Derived Infections • Colonized or incubated: influenza, pseudomonas, aspergillus • MTB reactivation • Candida	After Prophylaxis Stops • Pneumocystis • Herpesviruses: CMV, HSV, VZV • HBV • Listeria, Legionella, Nocardia, Toxoplasmosis • Community-Acquired: UTI, pneumonia, C. difficile	Community-Acquired Infections • Pneumonia • UTI • Influenza • Aspergillus • HBV • HCV
Nosocomial Infections • MRSA, VRE, ESBL/CRE • C. difficile • UTI • CLABIs • Pneumonia • Surgical site sepsis		

C. difficile, Clostideroides difficile; CLABIs, central-line associated blood stream infections; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESLB/CRE, extended spectrum beta-lactamase/carbapenem resistant enterobacteria; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; JC/PML, JC virus/progressive multifocal leukoencephalopathy; LCMV, lymphocytic choriomeningitis virus; MRSA, methicillin-resistant *staphylococcus aureus*; *MTB,* mycobacterium tuberulosis; PTLD, post-transplant lymphoproliferative disease; *T. cruzi,* Trypanosoma cruzi; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus; VZV, varicella zoster virus

Malignancy

Cancer is another common post-kidney transplant cause of mortality.[13,25] KTR have an increased risk of malignancy two to three times that of their age-matched and gender-matched counterparts within the general population, with the risk of developing conditions such as Kaposi's Sarcoma increasing by up to three hundred times.[26] Other malignancies with an increased incidence include non-melanoma skin

cancer, lip cancer, and those associated with a viral aetiology.[26-28] Risk factors for the development of cancer post-transplantation may be modifiable or non-modifiable, as well as being present pre-transplantation or accrued post-transplantation.[25] Non-modifiable risk factors include male gender, age >50, Caucasian race, viral infections (Epstein-Barr, human herpesvirus 8, hepatitis B or hepatitis C).[25] Modifiable risk factors include smoking, diabetes mellitus, and post-transplant immunosuppressant therapy.[25] While rare, donor-derived transmission of malignancy may also occur.[25]

Rarely does cancer occur within the first three months post-transplantation, and when present it is an uncommon cause of death within the first twelve months post-transplantation.[13] Rather, a continual increase in cancer-associated mortality is seen from one year post-transplantation onwards, with rates exceeding 25% by 20 years post-transplantation.[13,25] Despite being a long-term cause of mortality, the overall incidence of cancer-associated mortalities is lower than in previous decades.[13]

Death-Censored Graft Loss

Each of the risk factors discussed above contribute towards graft loss and/or may result in death of the KTR.[12,17] Death-censored graft loss, considered as allograft failure in a living KTR, may also be a consequence of the above discussed risk factors as well as having other risk factors.[12,17] Death-censored graft loss may be influenced by other factors such as delayed graft function (DGF), antibody (humoral) mediated rejection (ABMR), BK virus, disease recurrence, anaemia and calcineurin inhibitor toxicity.[12,17,29,30] These factors may contribute both independently and in association with one another, leading to accruement of multiple insults over time to culminate in graft loss.[12]

Delayed Graft Function

DGF is a well-established post-transplant outcome lacking for a universally accepted criterion, having over 10 definitions available.[31,32] Amongst its many definitions, it may be defined as dialysis-based, such as an acute kidney injury requiring dialysis within the first week post kidney transplantation, or creatinine-based: with an elevated creatinine >2.5mg/dL (>221.05 umol/L) at days 7 or 10 post-transplant.[31] DGF is more common in deceased donor KTR than living donor KTR, with an increasing incidence of DGF noted internationally.[29,33] When present, DGF is associated with increased incidence of graft loss and mortality, in both living and deceased donor KTR.[29,33]

Development of DGF is multifactorial in aetiology with both modifiable and non-modifiable risk factors, such as: increased recipient body mass index >25, prolonged cold-ischaemic times >12 hours, age of >50 years, and female gender, amongst a multitude of other risk factors.[29] Redfield et al.[29] further showed that African American ethnicity, whether being the donor or recipient, is a non-modifiable risk factor for developing DGF in living donor KTR. Despite recognition of DGF as a significant adverse outcome in international studies, South African data lacks elucidation of risk factors (e.g. donor genetic profiles) that may uniquely contribute to our own rates of DGF. As such, concern is raised regarding the potential for missed opportunities to identify risk factors and prevent undesirable outcomes

Graft Rejection

Graft rejection predisposes to graft failure, which may be T-cell mediated (TCMR) and/or ABMR.[34] An episode of rejection is further classified into three categories based on the timing of presentation: hyperacute: occurring within minutes to hours post-transplant, acute: occurring within days to months, and chronic: occurring

beyond at least one-year post-transplantation.[8,34] Each of these categories have characteristic histological findings allowing for classification via the (revised) Banff classification system.[34]

TCMR occurs most commonly in the acute phase post-transplantation.[34] Instances where TCMR occurs later can be due to factors such as ineffective immunosuppression (e.g. cases of patient non-compliance or part of specialist decision making) or acute illnesses causing an upregulation of the immune response.[34]

ABMR can be found at any stage post-transplant, though rarely does it occur in the hyperacute phase, a likely result of improved cross-matching techniques and donor-specific antibody (DSA) detection prior to transplantation.[34] Risk factors for ABMR include high panel-reactive antibodies, DSAs, human leukocyte antigen mismatches and incompatibility, blood group incompatibility and immunosuppression nonadherence.[30] The result is an anamnestic antibody response, culminating in ischaemic injury and cell death of the transplanted organ.[34]

Therapy for rejection depends on the type of rejection, severity, chronicity and response to previous therapy.[30,34] Therapy for refractory disease has yet to have a consensus on definitive treatment.[30,34] TCMR is treated based on its Banff classification, with the use of glucocorticoids and lymphocyte-depleting agents.[34] The responses to such therapies vary dependent on the Banff classification noted pre-treatment.[34] Treatment of ABMR is less standardized, with the need to target both clearance of present DSAs and complement, while also reducing the production of new antibodies.[30,34] Current methods include plasmapheresis with adjuvant therapies including intravenous immunoglobulins to clear existing DSAs and complement.[30,34]

Rituximab is used to mitigate antibody production, and agents such as eculizumab, bortezomib and antithymocyte globulin are used for cases refractory to rituximab.[30,34] Despite pre-transplant screening protocols, prevention strategies and rejection therapy, graft rejection remains a significant cause of morbidity, emphasising the necessity of more standardised evidence-based regimens.[30,34]

Graft rejection is a predisposing factor for graft failure, with some studies showing acute ABMR being an independent risk factor for death-censored graft failure, and a cause of 60% of late graft failures.[30,34] The concern of graft rejection associated graft failure losses extends beyond that of typical risk factors in our South African populace, a possible consequence of our high burden of HIV infection (HIV+).

Stock et al.[35] showed an increased rate of rejection in the HIV+ KTR of upwards of 2x their HIV negative (HIV-) counterparts. These findings were reinforced by Alfano et al.[36] in 2018 with a 2.8x graft rejection rate in the HIV+ KTR group. Rates of rejection in HIV+ KTR were found to be higher in cases that made use of cyclosporine; however, this study had a small cohort.[35,36] In a South African study Muller et al.[37] advocated for more potent immunosuppression in their study of HIV+ to HIV+ donor to recipients but still showed 19% acute rejection in their cohort.

Diabetes Mellitus

Diabetes mellitus (DM) is a heterogenous group of metabolic disorders with a resultant hyperglycaemia due to overproduction or underutilization of glucose.[38] Post-transplantation diabetes mellitus (PTDM), also referred to as new onset diabetes after transplantation or diabetes after transplantation, has a varied incidence in KTR of upwards of fifty percent in some cohorts.[39] PTDM should not be confused with transient post-transplant hyperglycaemia, which may occur due to

immunosuppressive therapies, rejection therapies, sepsis or post-surgical stress.[40] Instead, the term is reserved for diagnosis once the KTR has stable graft function on treatment and in the absence of infection or other stressors.[40] Development of PTDM includes both modifiable and non-modifiable risk factors, including but not limited to age, ethnicity, obesity, viral infections (hepatitis C, CMV) and immunosuppressive therapy (calcineurin inhibitors).[41]

PTDM follows the same diagnostic criteria as the general populace as set out by the American Diabetes Association, with an oral glucose tolerance test being the gold standard, however due to resource constraints the use of HbA1c is more convenient.[40,42] Reliance on HbA1c as a diagnostic test for DM is associated with limitations, such as decreased reliability within the first three months post-transplantation.[42] The use of HBA1c has been shown to be reliable from 12 months post-transplantation onwards.[42]

DM, whether existing pre-transplantation or as PTDM, is a risk factor for increases in both cardiovascular and sepsis related morbidity and mortality in KTR.[43] Presence of DM in KTR is associated with a five-fold increase in mortality from cardiovascular and sepsis related events relative to non-diabetic KTR.[39] Early identification and timeous management of PTDM is essential for the reduction of CVD events and improving outcomes of transplant recipients.[44]

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is the primary state hospital in the Gauteng province of South Africa to offer the service of renal transplantation. CMJAH serves an estimate of over 5 million people within the province, as well as performing renal transplants for state patients from the North-

West province and Limpopo. This provides an excellent opportunity to assess our post-transplantation outcomes relative to national and international findings.

This study aims to review the most common outcomes encountered in post-kidney transplant recipients at a state hospital in Gauteng, South Africa to improve surveillance and management protocols of potential complications, to optimize KTR care and prolong transplant kidney longevity. The primary objective of this study is to identify incidence of mortality and graft loss amongst KTR with potential factors that may influence these outcomes. Our secondary objectives to identify other adverse outcomes experienced by KTR that may have impact on quality of life and cost-effective health care.

Methodology

This study is a single centre retrospective record review of all first-time renal transplant recipients over the age of 18 years, who received their renal transplant at CMJAH, from 01 January 2012 to 31 January 2020. Ethics approval was received from the University of the Witwatersrand Human Research Ethics Committee (certificate number: M220874 – see Appendix 1). All patients will be allocated a random alpha-numeric value to ensure patient confidentiality.

The primary objective of this study is to describe outcome end points for the CMJAH renal transplant cohort, specifically:

1. Death of a recipient with and without graft loss
2. Graft loss as indicated by need for dialysis (dialysis may not have been provided due to rationing criteria)

Secondary objectives

1. To describe the incidence of adverse events in the CMJAH renal transplant cohort, specifically:
    a. Septic events (urosepsis vs non-urosepsis events)
    b. Diagnosis of malignancy
    c. Diagnosis of PTDM
    d. Rejection episodes
    e. Delayed graft function post-transplant
2. To describe demographic and immunosuppression data in the CMJAH renal transplant cohort
3. To compare HIV positive to HIV negative patients with respect to the above parameters

The baseline data collected on the KTR included demographics: age at transplant, sex, HIV status of recipient at transplantation, cause of the ESKD, induction and maintenance therapy, change of maintenance and indication, nature of the donor noted as living or deceased.

Presence or absence of delayed graft function was noted by the initiation of dialysis within seven days post-transplantation or a day 7 creatinine >221.05umol/L.[31]

Loss of graft function was represented by the ongoing need for dialysis post-transplant and assessed in terms of time elapsed post-transplant. Included in this group are those who experienced sepsis and required dialysis but did not regain function after the episode had resolved.

Rejection episodes were histologically classed in accordance with the modified/revised Banff criteria and detected at protocol biopsies of three or six months, one year, or non-protocol biopsies for renal decompensation.

Duration of hospital stay post-transplantation was noted with respect to aetiology if septic in origin (urosepsis related vs other septic cause).

The total number of admissions post-transplant was assessed according to time frame post-surgery, that is: within 3 months, 3-12 months, or more than 12 months and reason for admission, being either sepsis related: urosepsis vs other sepsis or non-sepsis related. Urosepsis was diagnosed based on the following findings:

- Presence of an organism with $\geq 10^5$ colony-forming units/mL on urine
- Leukocyturia as defined by >10/uL, with or without nitrites
- Culture negative urosepsis was defined as: urinary tract infection (UTI) symptoms such as dysuria, frequency, urgency, or graft tenderness and

resolution of symptoms with antibiotic therapy in the absence of urinary culture results (i.e. probable UTI)[45]

Other reasons for hospitalisation were noted and included non-sepsis related events: elective procedures, non-infectious renal dysfunction for workup, special investigations, etc.

Episodes of sepsis occurring and managed in an outpatient setting were assessed as urosepsis vs non-urosepsis related, in accordance with the above criterion and relative to the time of occurrence since transplantation, that is: within 3 months, 3-12 months, and more than 12 months.

Episodes of nosocomial sepsis were defined as infection occurring during hospital stay, 48 hours post-admission and not related to the primary cause for admission.[46] Episodes were further were divided into urological and non-urological infections.

Anaemia was defined as a haemoglobin <13.5g/dL in males and <12g/dL in females. PTDM was documented as an HBA1c ≥6.5% if ≥12 months post transplantation, a random plasma glucose >11.1 mmol/L, or the KTR was initiated on long-term anti-hyperglycaemic therapy despite paucity of documented information to support the diagnosis.[40] Malignancy was documented as per histological diagnosis and according to the time frame post-transplant.

A statistician will be consulted for advanced statistical analysis and data interpretation. All data captured in an excel spreadsheet will be exported to Strata 18 for analysis. After data cleaning – removing duplicates, checking for inconsistent/out of range data. Descriptive statistics- medians and interquartile ranges – will be used to describe the cohort with respect to continuous variables while frequencies and percentages were used to describe the cohort with respect to categorical variables.

Kaplan-meier curves were used to estimate time to death or graft loss and proportion of the transplant cohort surviving with a functioning graft at yearly intervals during follow-up. Kaplan-meier curves were used to estimate time to graft loss and proportion of the transplant cohort who had surviving grafts at yearly intervals during follow-up.

Mortality and graft loss will be determined as the number of patients in the cohort who died or required dialysis during post-transplant follow up, respectively, divided by the number of patients who received a renal transplant and presented as a percentage with 95% confidence intervals. Mortality and graft loss will be described overall and by HIV status using the X^2 test. Poisson regression with robust error variance was used to determine factors that were associated with mortality and graft post-transplant. Variables that have a p-value of less than 0.2 in univariable analyses will be included in the multivariable model up to a maximum of four variables with mortality and five variables with graft loss.

Ethical considerations

Permission was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, the Postgraduate Committee of the University of the Witwatersrand, the Head of the Renal department of CMJAH, and the Chief Executive Officer of CMJAH.

Funding

There will be no need for additional funding as this is a retrospective record review, and all data sought is kept in records within the renal transplant unit at CMJAH.

Strengths

Consistent data collection as all data to be collected by a single researcher

Limitations

Record keeping may impact on data available for collection.

Patients previously receiving a kidney transplant at CMJAH but subsequently moved to a different facility for ongoing care will limit available records.

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Chapter 2: Submissible Article

Authors guidelines

Intended journal

South African Journal of Medicine

Manuscript categories and requirements (as copied from the official website):

All submissions must meet the following requirements.

- Please ensure you have submitted a regular version of the manuscript i.e. full text with author details and an anonymised version (author details remove). Failure to do so will result in your manuscript being returned to you.
- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in Microsoft Word document file format.
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
- The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
- Disclosure of whether any artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) has been used in the production of submitted work.

Research articles

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly

summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may

have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Technical formatting guidelines are as follows:

General formatting guidelines

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

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References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
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    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Manuscript for submissible article

Title: Outcomes of Adult Kidney Transplant Recipients at Charlotte Maxeke Johannesburg Academic Hospital between 01 January 2012 and 31 January 2020

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Abstract

Background: Kidney transplantation is a lifeline for individuals with end-stage kidney failure, offering quality of life, financial and survival benefit over chronic dialysis. Kidney transplantation is complex and dependent on multiple donor and recipient factors. Ensuring longevity of future allografts requires understanding of limitations to previous allografts.

Objectives: Review the most common outcomes encountered in KTR at a state hospital in Gauteng, South Africa

Methodology: This was a single centre retrospective record review of all first-time adult renal transplant recipients from 01 January 2012 to 31st January 2020. Data collected included demographic and clinical parameters. Complications post-transplantation were noted. Outcome end points were recipient death and graft loss (defined by a need to return to dialysis).

Results: One-hundred and sixty-seven (167) patients over 18 years old received renal transplants at our facility between 1 January 2012 and 31 January 2020, 140 were included, of which 94 (67.1%) were male and 46 (32.9%) were female. The mean (SD) age at transplant was 41.9 years (10.5 years). Hypertension was noted as the principal aetiology for renal failure in 81 (57.9%) patients. One-hundred and twenty-eight (128, 91.4%) received a cadaveric kidney transplant and 12 (8.6%) received a kidney from a living donor. Median time to discharge was 18 days (IQR 11-32 days). 63 (45.0%) patients experienced delayed graft function, of which 45 (71%) received dialysis support. 49 (35%) patients experienced graft loss with a median time to loss of 30 months (IQR 6-52 months). Anaemia and delayed graft function were significant risk factors for graft loss, ($p<0.001$). Antibody-mediated rejection, T-cell mediated rejection and BK nephropathy all proved significant risk factors for graft loss ($p<0.001$, $p=0.002$, and $p=0.003$ respectively). Other complications included 39 (27.9%) KTR developed post-transplant diabetes, and 8 malignancies occurred in 7 (5.0%) KTR. Thirty-nine (27.9%) patients demised throughout the study period the primary cause of death was sepsis with 21 (53.9%) deaths.

Conclusion: Sepsis was a major cause of death and graft loss. Fifty-five percent (55%) of recipients had a functioning graft at 5 years. Further studies are required to determine factors influencing long term graft outcomes in our population.

Nomenclature

ABMR	Antibody (Humoral) Mediated Rejection
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CVD	Cardiovascular Disease
CI	Confidence Interval
DM	Diabetes Mellitus
DGF	Delayed Graft Function
EGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
HIV +	Human Immunodeficiency Virus Positive
HIV -	Human Immunodeficiency Virus Negative
IQR	Inter-Quartile Range
KTR	Kidney Transplant Recipient(s)
OPTN	Organ Procurement and Transplantation Network
PTDM	Post-Transplant Diabetes Mellitus
KRT	Kidney Replacement Therapy(ies)
TCMR	T-Cell Mediated Rejection
US	United States
UTI	Urinary Tract Infection(s)

Introduction

The burden of chronic kidney disease (CKD) is increasing globally, and South Africa is no exception.[1,2] Progression of CKD to end-stage kidney failure is often multifactorial in aetiology, encompassing both communicable and non-communicable disease in an aging population.[1,3] The multimorbidity which South Africa faces will likely continue to expand.[4] Thus adding to the potential seen in certain predictive models, suggesting CKD amongst the top 5 causes of years of life lost by 2040.[5] This expanding cohort with end-stage kidney disease (ESKD) is accompanied by an unmet demand for kidney replacement therapies, most notably in low- and middle-income countries.[3] The gold standard for ESKD is kidney transplantation, offering both quality of life and financial benefit.[6] Transplantation is not without risk and the KTR needs specialist monitoring to prevent morbidity, death and allograft loss.[7]

Despite South Africa being one of the most active proponents for renal transplantation on the African continent, our total transplantations are outmatched by those of more developed nations.[8] Mainly attributable to a primary reliance on deceased donors and resource constraints.[9,10] Thus longevity of existing allografts is a priority for all involved, to extend patient quality of life and reduce costs. Internationally KTR graft loss occurs primarily from cardiovascular disease (CVD) associated deaths.[11,12] This contrasts to other South African studies where sepsis is a primary cause of death and subsequent graft loss.[13] Graft loss in surviving KTR may be the result of an accumulation of risk factors and insults over time such as delayed graft function (DGF), antibody (humoral) mediated rejection (ABMR), BK nephropathy, disease recurrence, anaemia, and calcineurin inhibitor toxicities.[14,15]

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is the primary state hospital in the Gauteng province of South Africa to offer renal transplantation to the public sector for patients from Gauteng, North-West and Limpopo provinces. This study aims to review the most common outcomes encountered in KTR at a state hospital in Gauteng, South Africa.

Methodology

This study was a single centre retrospective record review of all first-time renal transplant recipients over the age of 18 years, at CMJAH, from 01 January 2012 to 31 January 2020. Ethics approval was received from the University of the Witwatersrand Human Research Ethics Committee (certificate number: M220874).

The primary objective of this study was to describe outcome end points for the CMJAH renal transplant cohort, specifically death of a recipient with and without graft loss; and Graft loss as indicated by need for dialysis.

Secondary objectives were to describe the incidence of adverse events in the CMJAH renal transplant cohort, specifically septic events (urosepsis vs non-urosepsis events), diagnosis of malignancy, diagnosis of post-transplant diabetes mellitus (PTDM), rejection episodes, delayed graft function post-transplant. To describe demographic and immunosuppression data in the CMJAH renal transplant cohort. To compare HIV positive (HIV +) to HIV negative (HIV -) patients with respect to the above parameters

The baseline data collected on the KTR included demographics: age at transplant, sex, HIV status of recipient at transplantation, cause of the ESKD, induction and maintenance therapy, change of maintenance and indication, nature of the donor noted as living or deceased.

Presence or absence of DGF was noted by the initiation of dialysis within seven days post-transplantation or a day 7 creatinine >221.05umol/L.[16] Loss of graft function was represented by the ongoing need for dialysis post-transplant and assessed in terms of time elapsed post-transplant.

Rejection episodes were histologically classed in accordance with the modified/revised Banff criteria.

Indication for hospital stay post-transplantation was noted with respect to aetiology if septic in origin (urosepsis related vs other septic cause).

Other reasons for hospitalisation were noted and included non-sepsis related events: elective procedures, non-infectious renal dysfunction for workup, special investigations, etc.

Episodes of sepsis occurring and managed in an outpatient setting were assessed, in accordance with the above criterion and relative to the time of occurrence since transplantation, that is: within 3 months, 3-12 months, and more than 12 months.

Anaemia was defined as a haemoglobin <13.5g/dL in males and <12g/dL in females. PTDM was documented as an HBA1c ≥6.5% if ≥12 months post transplantation, a random plasma glucose >11.1 mmol/L, or the KTR was initiated on long-term anti-hyperglycaemic therapy despite paucity of documented information to support the diagnosis.[17] Malignancy was documented as per histological diagnosis and according to the time frame post-transplant.

Statistical analysis and data interpretation was done in consultation with a statistician. All data captured in an excel spreadsheet was exported to Strata 18 for analysis. Descriptive statistics were used to describe the demographic and immunosuppressive characteristics of the cohort. Medians and interquartile ranges were used to describe continuous variables while frequencies and percentages were

used to describe both categorical variables as well as the occurrence of adverse events.

Kaplan-meier curves were used to estimate time to death or graft loss and proportion of the transplant cohort surviving with a functioning graft at yearly intervals during follow-up. Kaplan-meier curves were used to estimate time to graft loss and proportion of the transplant cohort who had surviving grafts at yearly intervals during follow-up.

Results

One hundred and sixty-seven patients over the age of 18 years received renal transplants at CMJAH between January 01st 2012 and January 31st, 2020. Twenty-seven patients were excluded from the study; 10 had received a previous transplant, and 17 had an incomplete dataset. The remaining 140 patients were included in this study.

Demographics and clinical characteristics of KTR

Patient demographics and baseline characteristics are shown in **Table 1**. Of 140 KTR, 94 (67.1%) were male. The mean (SD) age of KTR at time of transplant was 41.9 years (10.5 years). Ten (7.1%) patients were HIV positive at the time of transplant. Isolated hypertension was noted as a principal aetiology for renal failure in 81 (57.9%) patients and 44 (31.4%) patients had renal failure of unknown or undocumented aetiology. One hundred and twenty-eighty patients (91.4%) received a cadaveric kidney transplant and 12 (8.6%) received a kidney from a living donor. The median follow-up time of the cohort was 57 months (IQR 20.5 - 88.5 months).

Table 1: Demographic and clinical characteristics of the transplant cohort

Characteristic	n (%)
Age in years (mean, s.d)	41.9 (10.5)
Biological sex	
Female	46 (32.9)
Male	94 (67.1)
HIV status	
Negative	130 (92.9)
Positive	10 (7.1)
Cause of renal failure	
Isolated Hypertension	81 (57.9)
Unknown	44 (31.4)
Other*	15 (10.7)
Type of transplant	
Cadaver	128 (91.4)
Living	12 (8.6)
Median follow up time (months)	57 (IQR 20.5-88.5)

* Diabetes: 1 (0.7%), Hypertension and diabetes 1 (0.7%), Autosomal dominant polycystic kidney disease (ADPCKD) 3 (2.1%), Bilharzia 2 (1.4%), Lupus nephritis 2 (1.4%), Nephrosclerosis 1 (0.7%), Bladder injury 1 (0.7%), primary membranous glomerulonephritis 1 (0.7%), mesangioproliferative glomerulonephritis 2 (1.4%), malaria 1 (0.7%)

Immunosuppressive therapy: Induction and Maintenance Regimen

Table 2 details immunosuppressant regimens used in the treatment of our cohort with available data. Basiliximab was the most used induction agent, in 71 (50.7%) cases and Antithymocyte globulin (ATG) in 61 (43.6%) cases. One hundred and thirty-three patients (95.0%) were subsequently placed onto a regimen comprised of mycophenolate mofetil (MMF), tacrolimus and prednisone.

Eighty-two (58.6%) patients required a change of maintenance therapy. MMF was the first drug changed in the maintenance regimen in 47 (57.3%) cases. Diarrhoea was most the most common indication for agent switch from MMF with 26 (42.6%) cases reported.

Table 2: Immunosuppressant therapy

Characteristic	Category	n(%)
Immunosuppressant regimen	*Induction*	
	ATG	61 (43.6)
	Basilixumab	71 (50.7)
	ATG then Basilixumab	1 (0.7)
	Unknown	7 (5.0)
	Maintenance	
	MMF/Tacrolimus/Prednisone	133 (95.0)
	CYA/MMF/Prednisone	5 (3.6)
	Prednisone/MMF only	1 (0.7)
	AZA/CYA/Prednisone	1 (0.7)
	Patients requiring a maintenance change	
	No	58 (41.4)
	Yes	82 (58.6)
Initial drug changed in a maintenance regimen	MMF	47 (57.3)
	Tacrolimus	32 (39.0)
	CYA	3 (3.7)
Overall, most common maintenance drug changed or stopped	MMF	61 (48.4)
	Tacrolimus	40 (31.8)
	CYA	13 (10.3)
	AZA	12 (9.5)
MMF changed to	AZA	38 (62.3)
	ARAVA	10 (16.4)
	MFA	13 (21.3)
Listed indications for change of MMF	Diarrhoea	26 (42.6)
	Unknown	11 (18.0)
	BK nephropathy	10 (16.4)
	Leukopenia	8 (13.1)
	Planned pregnancy	3 (4.9)
	SVC syndrome	1 (1.6)
	Both leukopenia and diarrhoea	1 (1.6)
	MMF Colitis	1 (1.6)

ATG = antithymocyte globulin; AZA = azathioprine; CYA = cyclosporin A; MMF = mycophenolate mofetil; SVC syndrome = superior vena cava syndrome

Post-transplant outcomes

1) Immediate outcomes following engraftment

Table 3 details immediate outcomes following engraftment. Sixty-three (45.0%) KTR experienced DGF, of which 45 (71.4%) received acute dialysis. Thirty-six (25.7%) KTR had nosocomial urosepsis within the immediate post-transplantation period, 53 (37.9%) had an alternative nosocomial sepsis (non-urosepsis). The median time to discharge following graft implantation was 18 days (IQR 11-32 days).

Table 3: Immediate outcomes following engraftment

Variable		n(%)
Delayed graft function	No Yes	77 (55.0) 63 (45.0)
Delayed graft function that received KRT	No Yes Unknown	15 (23.8) 45 (71.4) 3 (4.5)
Number of patients with Urosepsis (n=140)	Yes No	36 (25.7) 104 (74.3)
Number of patients with Other sepsis (n=140)	Yes No	53 (37.9) 87 (62.1)
Nosocomial sepsis events	Urosepsis Other sepsis	53 (36.8) 91 (63.2)
Days to discharge	Median (IQR)	18 (11- 32)

2) Admissions and sepsis-related events

Table 4 depicts the subsequent admissions and sepsis events in various periods post-transplant.

Table 4: Subsequent admissions and sepsis related events in the post-transplant period

Post transplant period, (n = no. of KTR)	Up to 3 months (n = 140)	4 – 12 months (n = 127)	>12 months (n = 115)
Total number of admissions during the period, n (%)	161	291	464
Reason for admission Sepsis, n (%) Non-sepsis, n (%)	 49 (30.4) 112 (69.6)	 86 (29.6) 205 (70.5)	 197 (42.5) 267 (57.5)
Number of KTR admitted during the period	95 (67.9)	109 (85.8)	103 (89.6)
Median number of admissions per KTR, median (range)	2 (1 – 4)	2 (1 – 15)	3 (1 – 22)
Total number of KTR treated for sepsis in the outpatient setting, n (%)	33 (23.6)	65 (51.2)	81 (70.4)

3) Long term complications and outcomes

a) Kidney biopsy results

Protocol and non-protocol biopsy results at different time periods post-transplantation are shown in **table 5**

Table 5: Biopsy results among KTR cohort, N=140

Renal biopsy	Total KTRs who had a biopsy	Total Biopsies done	Histological pattern	Frequency (%)
Protocol 3-6 month	78	78	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	64 (82) 7 (9) 1 (1.3) 0 5 (6.4) 1 (1.3)
Protocol 12 month	69	69	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	47 (68.1) 10 (14.5) 4 (5.8) 2 (2.9) 3 (4.4) 3 (4.4)
Post-transplant <3months	53	68	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	40 (58.8) 14 (20.6) 8 (11.8) 3 (4.4) 0 3 (4.4)
Post-transplant 3-12 months	18	22	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	8 (36.4) 9 (40.9) 2 (9.1) 0 2 (9.1) 1 (4.5)
Post-transplant >12 months	31	59	None T-cell mediated Antibody mediated Both BK BK, TCMR and ABMR Suboptimal/rejected	35 (59.3) 8 (13.6) 6 (10.2) 5 (8.5) 1 (1.7) 1 (1.7) 3 (5.1)

TCMR, T-cell mediated rejection; ABMR, Antibody mediated rejection; BK, BK nephropathy; Both = TCMR and ABMR simultaneously

b) Post-transplant Diabetes Mellitus

Thirty-nine (27.9%) KTR developed post-transplant diabetes mellitus (PTDM) with a median time to onset of 10 months (IQR 3 – 52 months).

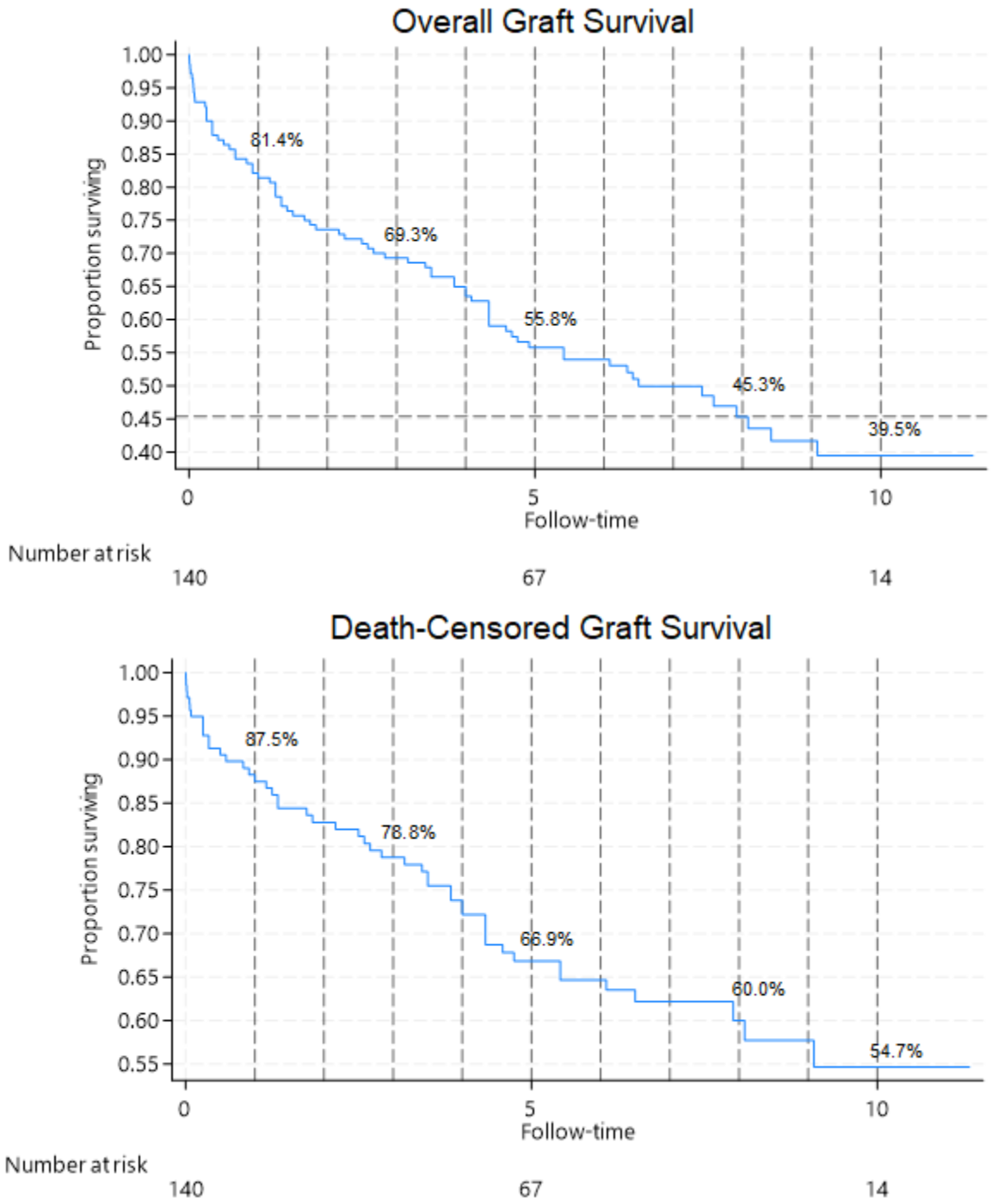
c) Malignancy

Eight malignancies occurred in 7 (5.0%) KTR. Two (25%) episodes of prostate cancer, squamous cell carcinoma and Kaposi sarcoma occurred. Papillary renal cell carcinoma and basal cell carcinoma, each accounting for 1 (12.5%) instance. 1 KTR developed both basal cell carcinoma and Kaposi sarcoma.

d) Patient and graft survival

Figure 1 is of Kaplan-Meier estimates showing overall and death-censored graft survivals. Forty-nine (35%) KTR experienced graft loss and 39 (27.9%) KTR demised. Kaplan-Meier estimates show death-censored graft loss at 1-, 3-, 5- and 8-years post-transplantation of 87.5% (CI 80.7-92.1%), 78.8% (CI 70.7-84.8%), 66.9% (CI 57.8-74.4%), and 60% (CI 49.8-68.8%) respectively. While Kaplan-Meier estimates for overall graft survival at 1-, 3-, 5-, and 8-years post-transplantation are 81.4% (CI 73.9-87.0%), 69.3% (CI 60.9-76.2%), 55.8% (CI 47.1-63.7%), and 45.3% (CI 35.8-54.3%) respectively.

Figure 1: Kaplan-Meier estimates depicting overall graft survival and death-censored graft survival measured in years



e) Factors associated with graft loss

Table 6 provides details of graft loss and **Table 7** expands on factors associated with graft loss in this cohort. Forty-nine (35%) KTR experienced graft loss, 14 (30.4%) were female and 35 (37.2%) were male. Median time to graft loss was 30 months (IQR 6-52 months). The median eGFR at time of graft loss was 10 ml/min/1.73m² (IQR 8-15 ml/min/1.73m²).

Twelve (33.3%) living and 45 (35.2%) cadaveric KTR had graft loss. Thirty-four (54%) of the 63 KTR who experienced DGF developed graft loss, univariable relative risk 2.77 (confidence interval (CI) 1.66-4.61), p= <0.001.

Forty-seven (58%) of the 81 KTR who had anaemia experienced graft loss, univariable relative risk 17.12 (CI 4.31-68.02), p<0.001. Six (60%) of the 10 HIV+ KTR had graft loss, p=0.039.

Of the 49 (35%) KTR who had graft loss, 27 (55.1%) experienced a biopsy confirmed rejection, p=0.004. When isolating for rejection type, 13 (68%) of the 19 KTR who had ABMR developed graft loss, univariable relative risk 4.36 (CI 2.15-8.86), p<0.001. Seventeen (48.6%) of the 35 KTR with TCMR developed graft loss, univariable relative risk 3.1 (CI 1.50-6.39), p=0.002. Graft loss occurred in 7 (77.8%) of the 9 KTR who developed BK nephropathy, univariable relative risk 4.96 (CI 2.39-10.27), p=0.003.

Table 6: Rates of graft loss

Variable	**n(%)**
Graft loss	
No	91 (65)
Yes	49 (35)
Time to graft loss (months, IQR)	30.0 (6-52)
Median eGFR at graft loss	10 (IQR 8-15)
Returned to dialysis	
No	11 (22.45)
Yes	33 (67.35)
Unknown	5 (10.2)

Table 7: Factors associated with graft loss among CMJAH renal transplant cohort

Variable	Univariable RR (95% CI)	p-value	Multivariable RR (95% CI	p-value
Age, median (IQR)	1.01 (0.98- 1.03)	0.570		
Biological sex Female Male	 1.00 1.22 (0.73- 2.04)	 0.440		
Transplant type Cadaver	 1.05 (0.46 – 2.44)	 0.901		
Delayed graft function	2.77 (1.66- 4.61)	<0.001	1.68 (1.08- 2.62)	0.023
Latest creatinine, median (IQR)	1.001 (1.000- 1.002)	<0.001	1.001 (1.000- 1.002	0.001
Anaemia	17.12 (4.31 – 68.02)	<0.001	11.37 (2.85- 45.33)	0.001
Urosepsis	1.07 (0.64-1.79)	0.800		
Other sepsis	1.00			
Diagnosis of malignancy	1.24 (0.51- 3.01)	0.637		
PTDM	1.00			
HIV status Positive	1.81 (1.03 – 3.19)	0.039	1.08 (0.46 – 2.52)	0.863
Rejections*	2.78 (1.38- 5.59)	0.004	1.41 (0.80- 2.50)	0.234
ABMR*	4.36 (2.15- 8.86)	<0.001	2.27 (1.28- 4.03)	0.005
TCMR*	3.10 (1.50-6.39)	0.002	1.84 (1.04- 3.25)	0.036
ABMR and TCMR*	5.74 (2.93- 11.23	0.002	1.84 (0.92- 2.62)	0.079
BK nephropathy*	4.96 (2.39- 10.27)	0.003	2.43 (1.39- 4.24)	0.002

*Included one at a time because of collinearity

f) Mortality and associated factors

Table 8 provides details of mortality rates and **Table 9** provides a breakdown of the death-associated parameters. Thirty-nine (28.6%) KTR demised: 14 (35.9%) females and 25 (64.1%) males. Thirty-four (87.2%) deaths were in cadaveric KTR and 5 (12.8%) from living donors. Median eGFR at time of death was 49 ml/min/1.73m² (IQR 15-76 ml/min/1.73m²). Twenty-three deaths (59%) occurred within a hospital setting.

Sepsis was the primary aetiology noted in 21 (53.9%) deaths. The most common septic cause of death was pneumonia with 8 (38.1%) cases. The second largest group of demises was of unknown aetiology 15 (38.5%), having occurred out of a hospital setting.

Increasing age was associated with an increased mortality, with a relative risk in the multivariable regression model of 1.04 (95% CI 1.02- 1.06).

Anaemia was a present in 31 (79.5%) KTR who demised, with a univariable relative risk 2.82 (CI 1.40-5.70), p=0.004.

DGF had been experienced by 14 (35.9%) KTR who demised, and graft loss was present in 15 (38.5%) KTR at the time of demise.

Table 8: Mortality rates

Died	
No	99 (70.7)
Yes	39 (27.9)
Unknown	2 (1.4)
Time to death (months)	15 (4- 52)
In-hospital death	
No	16 (41)
Yes	23 (59)
Aetiology of death (n=39)	
Sepsis	21 (53.9)
Unknown	15 (38.5)
Thromboembolic	2 (5.1)
Mob assault	1 (2.6)
Septic causes of death (n =21)	
Pneumonia	8 (38.1)
Sepsis of unknown origin	5 (23.8)
Urosepsis	3 (14.3)
Abdominal sepsis	3 (14.3)
Meningitis	1 (4.8)
Infective endocarditis	1 (4.8)
Median eGFR at time of death (months)	49 (IQR 15-76)
Median eGFR of surviving patients at last follow up (months)	35 (IQR 12-79)

Table 9: Factors associated with mortality among CMJAH renal transplant cohort

Variable	Univariable RR (95% CI)	p-value	Multivariable RR (95% CI	p-value
Age, median (IQR)	1.04 (1.02- 1.06)	<0.001	1.04 (1.02- 1.06)	<0.001
Biological sex Female Male	1.14 (0.66- 2.00) 1.00	0.633	1.51 (0.88- 2.63) 1.00	0.145
Transplant type Cadaver	1.00		--	--
Delayed graft function	1.00		1.00	
Latest creatinine, median (IQR)	1.000 (0.999-1.000)	0.530	--	---
Anaemia	2.82 (1.40- 5.70)	0.004	3.21 (1.54- 6.69)	0.002
Urosepsis	1.00		--	--
Other sepsis	1.00		--	--
Diagnosis of malignancy	1.00		--	--
PTDM	1.00		--	--
HIV status Positive	1.08 (0.40- 2.92)	0.874	--	--
Graft loss	1.16 (0.67- 2.00)	0.592	--	--
Rejections	1.00		--	--
ABMR	1.08 (0.46- 2.57)	0.855	--	--
TCMR	1.00		--	--
ABMR and TCMR rejection	1.25 (0.45- 3.49)	0.674	--	--
BK Nephropathy	1.00		--	--

g) Comparison of outcomes between HIV positive to HIV negative recipients

Table 10 shows the characteristics and adverse events between HIV status. HIV- cohort had a median age of 42 years (IQR 34 – 49 years) at transplantation, with a median age of 48 years (IQR 39 – 52 years) amongst the HIV+ cohort. Five (50%) HIV+ KTR were males and 89 (68.5%) males were HIV-.

DGF was present in 5 (50%) of the HIV+ KTR and 58 (44.6%) of the HIV- KTR. Urosepsis occurred in all 10 (100%) of the HIV+ and 91 (70%) of the HIV- KTR.

PTDM developed in 2 (20%) HIV+ and 37 (28.5%) HIV- KTR. Malignancy developed in 1 (10%) HIV+ and 6 (4.6%) HIV- KTR.

Graft loss was present in 6 (60%) of the HIV + and 43 (33.1%) of the HIV- cohort. The HIV+ KTR had 3 (30%) demises, with 36 (27.7%) amongst the HIV- KTR.

Table 10: Characteristics and adverse events by HIV status

Variable	HIV positive (N=10)	HIV negative (N=130)	Fischer's exact X^2 p-value
Age, median (IQR)	48.5 (39 - 52)	42 (34 – 49)	0.153*
Biological male sex	5 (50.0)	89 (68.5)	0.297
Living donor transplant	1 (10.0)	11 (8.5)	1.000
Delayed graft function	5 (50.0)	58 (44.6)	0.754
Latest creatinine, median (IQR)	401 (122 - 484)	141 (97 – 384)	0.141*
Anaemia	6 (60.0)	75 (57.7)	1.000
Any urosepsis	10 (100)	91 (70.0)	0.062
Other sepsis	8 (80.0)	101 (77.7)	0.866
Diagnosis of malignancy	1 (10.0)	6 (4.6)	0.412
PTDM	2 (20.0)	37 (28.5)	0.726
Total rejection episodes, median (IQR)	1 (0- 2)	0 (0- 1)	0.366
Graft loss	6 (60.0)	43 (33.1)	0.098
Died	3 (30.0)	36 (27.7)	1.000

*ranksum p-value

Discussion

This retrospective record review assessed the outcomes of KTR with their first kidney transplant occurring between January 1st, 2012, and January 31st, 2020, at the renal transplant unit in CMJAH.

One-hundred and sixty-seven KTR met study requirements with 140 eligible for data collection and interpretation. Ninety-four (67.1%) KTR were male and 46 (32.9%) were female, with a mean (SD) age at time of transplantation of 41.9 years (10.5). In the United States (US) the Organ Procurement and Transplantation Network (OPTN) shows most kidney transplants occur in patients aged 50-64 years, with the 35–49-year age group previously being the second most common group.[18] This is in keeping with an aging society requiring KRT.[11] In contrast a local study also noted younger ages (38 years) at transplantation.[13] This discrepancy is likely the result of strict dialysis rationing criteria due to resources limitations, thus younger patients with a better functional baseline are favoured in the public sector.[19] This can be corroborated by the South African renal registry with public health care patients getting some form of KRT at a younger age compared to our private health care patients.[21] Males are the predominant gender transplanted when considering both local and US data.[13,18]

Hypertension was the principal aetiology for ESKD in our cohort, in keeping with the South African renal registry, however contrasting the OPTN which shows diabetes as the principal aetiology in the US.[18,20] A possible explanation for this discrepancy may lie between private and public health care causes of ESKD in South Africa, with diabetes being more common in private health care.[20] Again, due to rationing criteria for dialysis, diabetics are less likely to qualify to receive KRT. A limiting factor for the discrepancy is the burden of unknown cause of renal failure at time of diagnosis, that is both appreciated in our findings and other South African data.[20]

Cadaveric kidney donors were the most transplanted, a finding appreciated both locally and internationally. [13,18]

Median follow up was 4.8 years (IQR 1.7-7.4 years). This is lower than internationally with a median of 7.2 years (IQR 4.2–11) for adults (>18 years) and a median of 7.8 years (IQR, 3.3–13.9 years) when taking all age groups into consideration.[11,14]

The most common induction agent used in CMJAH was basiliximab (50.7%). The OPTN shows a clear favouring of T-cell-depleting agents over interleukin 2 receptor antagonists in the US.[18] In line with guidelines our unit risk stratifies patients at time of transplantation to determine which induction agent is used.[21]

The most used maintenance regimen post-transplantation consisted of MMF, tacrolimus and prednisone in 133 (95%) KTR. US data shows the same predilection for this triple therapy as a maintenance regimen, in keeping with current guidelines.[18,21] MMF was most often the initial drug (57.3%) as well as the most common drug changed (48.4%). Diarrhoea was the principal indication for MMF switch (42.6%). Deng et al[22] comparing MMF to calcineurin inhibitors in maintenance therapy showed that diarrhoea is a common adverse outcome.

DGF was an immediate outcome shown to have occurred in 45% of our cohort, higher than what was seen from Davidson et al [13] (21.4%) in a local study or in the OPTN (26.1%).[18] As 91.4% of our KTR had a deceased donor, this could account for the high prevalence of DGF in our cohort. Other known risk factors not included in

our study that may have had implications on the development of DGF include prolonged cold ischaemic times, increased BMI >25 and African ethnicity.[23]

In the immediate post-transplantation period, urosepsis was present in 36 (25.7%) KTR with a total of 53 (36.8%) episodes. Fifty-three (37.9%) KTR developed a non-urosepsis infection with a total of 91 (63.2%) episodes. One international study showed 47% of KTR develop a bacterial infection within the first month, urinary tract infections (UTI) were the most common and had an average of 58 days to onset.[24] Locally others have found sepsis rates of 33.3% within the post-transplantation period.[13] However, sepsis rates in the peri-operative period varies greatly between facilities, and while UTIs are amongst the most common early post-transplant complication the incidence is variable.[22,24,25]

Median time to discharge following graft implantation was 18 days (IQR 11-32 days) within our cohort. Another South African centre has shown a median time to discharge of 13 days (IQR 10–18 days) and internationally studies document shorter length of stays post-transplant with median time to discharge of 8 days (IQR: 7–13 days).[13,26] A likely contributor to our longer length of stay is our post-transplant sepsis rate.

Ninety-five (67.9%) KTR required readmission with the first 3-months post-transplantation and 109 (85.8%) were readmitted within the 4-to-12-month period. While most admissions had non-septic indications (elective procedures, non-infectious renal dysfunction for workup, special investigations, etc), sepsis accounted for 30.4% of admissions within the first 3 months and 29.6% within the subsequent 4-to-12-month period post-transplant. Weeda et al[27] found infectious aetiologies made up to half of their top 10 indications for an admission, however of these sepsis accounted for 16.5% of admissions. Their patient hospital readmission rates within the first 90 days post-transplant ranged from 24.4%-40.7% and 24.8-36.5% between the 90-to-365-day period.[27] The discrepancy between patient readmissions rates is likely contributed to by the incidence of sepsis we experience. Factors not considered in this study that may have contributed to readmission within the first year period include: BMI >35 and underlying valvular heart disease.[27]

A total of 147 protocol biopsies were performed: 78 between 3 and 6 months, and 69 at 12 months post-transplant. Cumulatively, 111 (75.5%) biopsies did not demonstrate any form of rejection. TCMR was most identified with 7 (9%) and 10 (14.5%) episodes, at 3-to-6-months and 12 months respectively. These low detection rates are corroborated by Garcia-Lopez et al[28] demonstrating low detection rates of rejection with the use of protocol biopsies.

Renal biopsies done as per clinical indication totalled 149; 68 within 3 months post-transplantation, 22 between the 4-to-12-month period, and a further 59 >12 months. TCMR was the predominant finding at all intervals with 14 (20.6%), 9 (40.9%) and 8 (13.6%) episodes at the <3 month, 4-to-12-month, and >12 months periods respectively. ABMR was the second most common at all intervals with 8 (11.8%), 2 (9.1%) and 6 (10.2%) episodes at the <3 month, 4-to-12-month and >12 months periods. TCMR is more common in the first year post-transplant than ABMR which is noted both internationally and locally.[13,29] The incidence of ABMR is unexpectedly lower than local findings but within some international rates of 3-12% within the 1st year and 7.5%-20.1% reported beyond the first year up to 10 years post-transplant.[13,29]

Thirty-nine (27.9%) KTR developed PTDM with a median time to onset of 10 months. The incidence of PTDM is known to have variation depending on non-modifiable and modifiable risk factors, as well as post-transplant therapies including calcineurin inhibitors and corticosteroids.[30,31] Vincenti et al[32] in the DIRECT trial showed a PTDM incidence of 33.6% in the tacrolimus arm at 6 months. Both tacrolimus and corticosteroids were initially present in the maintenance therapy of our cohort (95%) and could account for a large burden of the PTDM. However, other known risk factors such as BMI and family history of type 2 diabetes were not considered in this study and may have contributed.[31]

Eight instances of malignancy occurred in 7 (5.0%) KTR. Despite the well-documented increased incidence of malignancy in transplant recipients, this low level of malignancy burden may be the result of the short period of follow up, as malignancy is associated with long-lived KTR.[33]

Thirty-nine (27.9%) KTR demised with a median time to demise of 15 months (IQR 4-52 months) and median eGFR at death was 49 ml/min/1.73m² (IQR 15-76 ml/min/1.73m²). Sepsis was the most common aetiology of death (53.9%). These findings correlate with existing South African literature regarding mortality of KTR in the public sector, but contrast with international findings of cardiovascular events as the leading cause of mortality.[11,13,34] However, our study has a bias in that causes of mortality were inferred from hospital records of the KTR demises and not post-mortem results. Additionally, some documentation was incomplete, hindering the accurate assessment of mortality as 15 (38.5%) KTR demised of unknown aetiology. Other explanations for the discrepancy of mortality include younger age at transplant than internationally, a high incidence of communicable diseases within South Africa, socioeconomic factors and availability of resources in resource-constrained facilities.

Anaemia was a significant risk factor identified in both graft loss ($p<0.001$) and mortality ($p=0.004$) in our cohort. An already established risk factor for graft loss, CVD and increased mortality in KTR, anaemia has varied impact on the KTR.[15,35] The overall effect of anaemia on the KTR may further be dependent on the timing of onset relative to the post-transplant period and severity of anaemia.[15,35,36] Due to the nature of this study we did not account for timing to onset, severity, or cause of anaemia in the KTR.

Graft loss occurred in 49 (35%) KTR, with a median time to loss of 30 months (IQR 6-52) and median eGFR at graft loss of 10 ml/min/1.73m² (IQR 8-15 ml/min/1.73m²). The notable risk factors for graft loss were ABMR, TCMR, BK nephropathy, anaemia and DGF. DGF as an independent risk factor afforded a univariable relative risk of 2.77 (CI 1.66-4.61), p= <0.001. Our findings are consistent with other existing data supporting DGF as an independent risk factor for graft loss.[23,37]

Rejection was another significant cause of graft loss in our cohort, with the detection of ABMR being the most significant, $p <0.001$. TCMR and BK nephropathy were also significant factors for graft loss with $p=0.002$ and $p=0.003$ respectively. This is in keeping with established knowledge of the impact of rejection on graft loss.[29,38] Importantly, each rejection episode was included one at a time due to collinearity, and the compounding impact of multiple types of rejection over a period within a single KTR was not accounted for. The time frame in which the rejection occurred relative to the time of graft loss was not accounted for, offering the potential for accumulation of other ailments that may have contributed to graft loss.

Our overall graft survival estimates fall short of international expectations, with a 5-year survival of 55.8% relative to some international findings upwards of 80%.[14,18] When censoring for death as a cause of graft loss, there is an appreciable reduction in the rate of graft loss over the years post-transplantation. However, our death-censored graft loss findings still fall short, with 66.9% 5-year survival relative to 80% found both locally and internationally.[13,14] Suggesting that not only is death a primary cause of allograft loss in our setting, with higher incidence than seen elsewhere, but that other factors playing a critical role in patient survival with allograft loss also contribute significantly.

One-hundred and thirty (92.9%) KTR were HIV- and 10 (7.1%) HIV+ at transplantation. We found no significant differences between the two groups in our cohort however the HIV+ cohort was very small. Internationally there appears to be a higher incidence of rejection in the HIV+ KTR cohorts, as much as 2x their HIV- counterparts.[39,40] These increased rejection rates showed an association with the use of cyclosporine and deceased donor KTR.[39] This study found the majority of recipients were on a tacrolimus based regimen, thus offering a potential answer for the lack of discrepancy between the two groups. A factor not in keeping would be the high deceased donor transplant rate that would have been expected to confer a risk of allograft rejection.[39]

Conclusion

Graft loss and death of the KTR at CMJAH were higher when compared to both local and international trends. With death being a significant cause of graft loss in our cohort and most commonly from sepsis related conditions. However, more research is needed to further evaluate the unidentified causes of KTR demise in our cohort as well as mitigating factors that may be acted on to reduce the incidence of morbidity, mortality and allograft loss.

Limitations

This study acknowledges several limitations. This is a single centre, retrospective record review with a small cohort. Patient numbers between HIV+ and HIV- KTR, as well as living and deceased KTR cohorts were too small for significant comparison. The study was an overview of outcomes within the centre and did not obtain all the variables related to underlying risk factors.

Recommendations

Digitization of data may assist in standardizing collection of pertinent data, longevity of information and ease accessibility for future information if needed.

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Appendix 1: Ethics committee approval certificate and faculty protocol approval letter

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr KD Schnaar
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Medical School
University

E-mail: kyleds@gmail.com

CC: Supervisor: Dr N Diana and Professor G Paget
<ninadiana1@gmail.com>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/11/07

REF: R14/49

PROTOCOL NO: **M220874** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Review of adult kidney transplant recipients at Charlotte Maxeke Johannesburg Academic Hospital, between January 2012 and January 2020*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr KD Schnaar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220874

NAME: (Principal Investigator)	Dr KD Schnaar
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*Review of adult kidney transplant recipients at Charlotte Maxeke Johannesburg Academic Hospital, between January 2012 and January 2020*
DATE CONSIDERED:	2022/08/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr N Diana and Professor O Paget
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/11/07

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

08/11/2022
Date

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
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Reference: Mrs Sandra Benn
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20 May 2022
Person No: 351118
PAG

Dr KD Schnaar
122 Roberts Avenue
Kensington
2094
South Africa

Dear Dr Kyle Schnaar

Master of Medicine in Internal Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Review of Adult Kidney Transplant Recipients at Charlotte Maxeke Johannesburg Academic Hospital Between January 2012 to January 2020* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 2: Turnitin Originality Report

Outcomes of Adult Kidney Transplant Recipients at Charlotte Maxeke Johannesburg Academic Hospital between 01 January 2012 and 31 January 2020 by Dr Kyle Schnaar Mmed.docx

ORIGINALITY REPORT

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Appendix 3: Tables and Figures

Table A: Sepsis associated with time post renal transplantation

Early-onset	Peak Immunosuppression	Late-Onset
Donor-Derived Infections • HCV, HBV, T.Cruzi, LCMV, Bacteraemia, endemic mycosis	On Prophylaxis • HCV • Polyomaviruses (BK virus) • Cryptococcus neoformans • MTB • Strongyloides • Leishmania • PTLD	Opportunistic infections • CMV • JC/PML • PTLD/EBV • Nocardia
Recipient-Derived Infections • Colonized or incubated: influenza, pseudomonas, aspergillus • MTB reactivation • Candida	After Prophylaxis Stops • Pneumocystis • Herpesviruses: CMV, HSV, VZV • HBV • Listeria, Legionella, Nocardia, Toxoplasmosis • Community-Acquired: UTI, pneumonia, C. difficile	Community-Acquired Infections • Pneumonia • UTI • Influenza • Aspergillus • HBV • HCV
Nosocomial Infections • MRSA, VRE, ESBL/CRE • C. difficile • UTI • CLABIs • Pneumonia • Surgical site sepsis		

C. difficile, Clostideroides difficile; CLABIs, central-line associated blood stream infections; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESLB/CRE, extended spectrum beta-lactamase/carbapenem resistant enterobacteria; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; JC/PML, JC virus/progressive multifocal leukoencephalopathy; LCMV, lymphocytic choriomeningitis virus; MRSA, methicillin-resistant *staphylococcus aureus*; *MTB,* mycobacterium tuberulosis; PTLD, post-transplant lymphoproliferative disease; *T. cruzi,* Trypanosoma cruzi; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus; VZV, varicella zoster virus

Table 1: Demographic and clinical characteristics of the transplant cohort

Characteristic	n(%)
Age in years (mean, s.d)	41.9 (10.5)
Biological sex	
Female	46 (32.9)
Male	94 (67.1)
HIV status	
Negative	130 (92.7)
Positive	10 (7.1)
Cause of renal failure	
Isolated Hypertension	81 (57.9)
Unknown	44 (31.4)
Other*	15 (10.7)
Type of transplant	
Cadaver	128 (91.4)
Living	12 (8.6)
Median follow up time (months)	57 (IQR 20.5-88.5)

* Diabetes: 1 (0.7%), Hypertension and diabetes 1 (0.7%), Autosomal dominant polycystic kidney disease (ADPCKD) 3 (2.1%), Bilharzia 2 (1.4%), Lupus nephritis 2 (1.4%), Nephrosclerosis 1 (0.7%), Bladder injury 1 (0.7%), primary membranous glomerulonephritis 1 (0.7%), mesangioproliferative glomerulonephritis 2 (1.4%), malaria 1 (0.7%)

Table 2: Immunosuppressant Therapy

Characteristic	Category	n(%)
Immunosuppressant regimen	*Induction*	
	ATG	61 (43.6)
	Basilixumab	71 (50.7)
	ATG then Basilixumab	1 (0.7)
	Unknown	7 (5.0)
	Maintenance	
	MMF/Tacrolimus/Prednisone	133 (95.0)
	CYA/MMF/Prednisone	5 (3.6)
	Prednisone/MMF only	1 (0.7)
	AZA/CYA/Prednisone	1 (0.7)
	Patients requiring a maintenance change	
	No	58 (41.4)
	Yes	82 (58.6)
Initial drug changed in a maintenance regimen	MMF	47 (57.3)
	Tacrolimus	32 (39.0)
	CYA	3 (3.7)
Overall, most common maintenance drug changed or stopped	MMF	61 (48.4)
	Tacrolimus	40 (31.8)
	CYA	13 (10.3)
	AZA	12 (9.5)
MMF changed to	AZA	38 (62.3)
	ARAVA	10 (16.4)
	MFA	13 (21.3)
Listed indications for change of MMF	Diarrhoea	26 (42.6)
	Unknown	11 (18.0)
	BK nephropathy	10 (16.4)
	Leukopenia	8 (13.1)
	Planned pregnancy	3 (4.9)
	SVC syndrome	1 (1.6)
	Both leukopenia and diarrhoea	1 (1.6)
	MMF Colitis	1 (1.6)

ATG = anti-thymocyte globulin; AZA = azathioprine; CYA = cyclosporin A; MMF = mycophenolate mofetil; SVC syndrome = superior vena cava syndrome

Table 3: Immediate Outcomes

Variable		n(%)
Delayed graft function	No Yes	77 (55.0) 63 (45.0)
Delayed graft function that received KRT	No Yes Unknown	15 (23.8) 45 (71.4) 3 (4.5)
Number of patients with Urosepsis (n=140)	Yes No	36 (25.7) 104 (74.3)
Number of patients with Other sepsis (n=140)	Yes No	53 (37.9) 87 (62.1)
Nosocomial sepsis events	Urosepsis Other sepsis	53 (36.8) 91 (63.2)
Days to discharge	Median (IQR)	18 (11- 32)

Table 4: Subsequent admissions and sepsis related events in the post-transplant period

Post transplant period, (n = no. of KTR)	Up to 3 months (n = 140)	4 – 12 months (n = 127)	>12 months (n = 115)
Total number of admissions during the period, n (%)	161	291	464
Reason for admission Sepsis, n (%) Non-sepsis, n (%)	 49 (30.4) 112 (69.6)	 86 (29.6) 205 (70.5)	 197 (42.5) 267 (57.5)
Number of KTR admitted during the period	95 (67.9)	109 (85.8)	103 (89.6)
Median number of admissions per KTR, median (range)	2 (1 – 4)	2 (1 – 15)	3 (1 – 22)
Total number of KTR treated for sepsis in the outpatient setting, n (%)	33 (23.6)	65 (51.2)	81 (70.4)

Table 5: Graft rejections among CMJAH transplant cohort, N=140

Renal biopsy	Total KTRs who had a biopsy	Total Biopsies done	Histological pattern	Frequency (%)
Protocol 3-6 month	78	78	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	64 (82) 7 (9) 1 (1.3) 0 5 (6.4) 1 (1.3)
Protocol 12 month	69	69	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	47 (68.1) 10 (14.5) 4 (5.8) 2 (2.9) 3 (4.4) 3 (4.4)
Post-transplant <3months	53	68	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	40 (58.8) 14 (20.6) 8 (11.8) 3 (4.4) 0 3 (4.4)
Post-transplant 3-12 months	18	22	None T-cell mediated Antibody mediated Both BK Suboptimal/rejected	8 (36.4) 9 (40.9) 2 (9.1) 0 2 (9.1) 1 (4.5)
Post-transplant >12 months	31	59	None T-cell mediated Antibody mediated Both BK BK, TCMR and ABMR Suboptimal/rejected	35 (59.3) 8 (13.6) 6 (10.2) 5 (8.5) 1 (1.7) 1 (1.7) 3 (5.1)

TCMR, T-cell mediated rejection; ABMR, Antibody mediated rejection; BK, BK nephropathy; Both = TCMR and ABMR simultaneously

Table 6: Rates of graft loss

Variable	n(%)
Graft loss	
No	91 (65)
Yes	49 (35)
Time to graft loss (months, IQR)	30.0 (6-52)
Median eGFR at graft loss	10 (IQR 8-15)
Returned to dialysis	
No	11 (22.45)
Yes	33 (67.35)
Unknown	5 (10.2)

Table 7: Factors associated with graft loss among CMJAH renal transplant cohort

Variable	Univariable RR (95% CI)	p-value	Multivariable RR (95% CI	p-value
Age, median (IQR)	1.01 (0.98- 1.03)	0.570		
Biological sex				
Female	1.00			
Male	1.22 (0.73- 2.04)	0.440		
Transplant type				
Cadaver	1.05 (0.46 – 2.44)	0.901		
Delayed graft function	2.77 (1.66- 4.61)	<0.001	1.68 (1.08- 2.62)	0.023
Latest creatinine, median (IQR)	1.001 (1.000- 1.002)	<0.001	1.001 (1.000- 1.002	0.001
Anaemia	17.12 (4.31 – 68.02)	<0.001	11.37 (2.85- 45.33)	0.001
Urosepsis	1.07 (0.64-1.79)	0.800		
Other sepsis	1.00			
Diagnosis of malignancy	1.24 (0.51- 3.01)	0.637		
PTDM	1.00			
HIV status Positive	1.81 (1.03 – 3.19)	0.039	1.08 (0.46 – 2.52)	0.863
Rejections*	2.78 (1.38- 5.59)	0.004	1.41 (0.80- 2.50)	0.234
ABMR*	4.36 (2.15- 8.86)	<0.001	2.27 (1.28- 4.03)	0.005
TCMR*	3.10 (1.50-6.39)	0.002	1.84 (1.04- 3.25)	0.036
ABMR and TCMR*	5.74 (2.93- 11.23	0.002	1.84 (0.92- 2.62)	0.079
BK nephropathy*	4.96 (2.39- 10.27)	0.003	2.43 (1.39- 4.24)	0.002

*Included one at a time because of collinearity

Table 8: Mortality rates

Died	
No	99 (70.7)
Yes	39 (27.9)
Unknown	2 (1.4)
Time to death (months)	15 (4- 52)
In-hospital death	
No	16 (41)
Yes	23 (59)
Aetiology of death (n=39)	
Sepsis	21 (53.9)
Unknown	15 (38.5)
Thromboembolic	2 (5.1)
Mob assault	1 (2.6)
Septic causes of death (n =21)	
Pneumonia	8 (38.1)
Sepsis of unknown origin	5 (23.8)
Urosepsis	3 (14.3)
Abdominal sepsis	3 (14.3)
Meningitis	1 (4.8)
Infective endocarditis	1 (4.8)
Median eGFR at time of death (months)	49 (IQR 15-76)
Median eGFR of surviving patients at last follow up (months)	35 (IQR 12-79)

Table 9: Factors associated with mortality among CMJAH renal transplant cohort

Variable	Univariable RR (95% CI)	p-value	Multivariable RR (95% CI	p-value
Age, median (IQR)	1.04 (1.02- 1.06)	<0.001	1.04 (1.02- 1.06)	<0.001
Biological sex Female Male	 1.14 (0.66- 2.00) 1.00	 0.633	 1.51 (0.88- 2.63) 1.00	 0.145
Transplant type Cadaver Living	 1.00 1.57 (0.75 – 3.25)	 0.228	 -- 	 --
Delayed graft function	1.00		1.00	
Latest creatinine, median (IQR)	1.000 (0.999-1.000)	0.530	--	---
Anaemia	2.82 (1.40- 5.70)	0.004	3.21 (1.54- 6.69)	0.002
Urosepsis	1.00		--	--
Other sepsis	1.00		--	--
Diagnosis of malignancy	1.00	0.461	--	--
PTDM	1.00		--	--
HIV status Positive	 1.08 (0.40- 2.92)	 0.874	 --	 --
Graft loss	1.16 (0.67- 2.00)	0.592	--	--
Rejections	1.00		--	--
ABMR	1.08 (0.46- 2.57)	0.855	--	--
TCMR	1.00		--	--
ABMR and TCMR rejection	1.25 (0.45- 3.49)	0.674	--	--
BK Nephropathy	1.00		--	--

Table 10: Characteristics and adverse events by HIV status

Variable	HIV positive (N=10)	HIV negative (N=130)	Fischer's exact X^2 p-value
Age, median (IQR)	48.5 (39 - 52)	42 (34 – 49)	0.153*
Biological male sex	5 (50.0)	89 (68.5)	0.297
Living donor transplant	1 (10.0)	11 (8.5)	1.000
Delayed graft function	5 (50.0)	58 (44.6)	0.754
Latest creatinine, median (IQR)	401 (122 - 484)	141 (97 – 384)	0.141*
Anaemia	6 (60.0)	75 (57.7)	1.000
Any urosepsis	10 (100)	91 (70.0)	0.062
Other sepsis	8 (80.0)	101 (77.7)	0.866
Diagnosis of malignancy	1 (10.0)	6 (4.6)	0.412
PTDM	2 (20.0)	37 (28.5)	0.726
Total rejection episodes, median (IQR)	1 (0- 2)	0 (0- 1)	0.366
Graft loss	6 (60.0)	43 (33.1)	0.098
Died	3 (30.0)	36 (27.7)	1.000

*ranksum p-value

Figure 1: Kaplan-Meier estimates depicting overall graft survival and death-censored graft survival measured in years