EVALUATION OF POTENTIAL KIDNEY DONORS

AND OUTCOMES POST-DONATION AT

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

(1983 – 2015)

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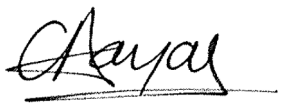
A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2019

DECLARATION

I, Chandni Dayal, hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the publishable format as recognised by the Faculty of Health Sciences. I further declare that this work has not been submitted before for any degree or examination at this or any other University.



3rd day of June, 2019

For my parents,

Prakash and Nirmal Dayal

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS RESEARCH

1. Awarded best poster presentation at the South African Renal Society Congress, Cape Town, 11 September 2016

    - Published abstract resulting: Dayal C, Diana N, Davies M, Meyers AM, Paget G. Failure to launch: Exclusion from living kidney donation at Charlotte Maxeke Johannesburg Academic Hospital (1983-2015). African Journal of Nephrology 2016;19:48.

2. Oral presentation at the South African Renal Society Congress, Cape Town, 9-11 September 2016

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3. Oral presentation to the Wits Donald Gordon Medical Centre Renal unit, Johannesburg, 13 October 2016

4. Oral presentation to the Charlotte Maxeke Johannesburg Academic Hospital Department of Internal Medicine, Johannesburg, 10 February 2017

ETHICAL CONSIDERATIONS

Permission for this retrospective study was obtained from Prof. G. Paget (Head of Nephrology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital), Ms. G. Bogoshi (Chief Executive Officer, Charlotte Maxeke Johannesburg Academic Hospital), and the Human Research Ethics Committee of the University of Witwatersrand (Clearance number M150923).

ABSTRACT

Background

Living kidney donation has emerged as a key therapeutic modality for end-stage kidney disease due to the global chronic shortage of renal allografts. However, the potential benefits to the recipient of a living donor kidney must be balanced against donor safety. In demographically diverse populations, there is a paucity of data regarding the living donor evaluation process and outcomes following donation.

Objectives

This study was undertaken to describe donation patterns, characterise reasons for non-donation and evaluate long-term morbidity and mortality following living kidney donation in the South African context.

Methods

A retrospective analysis of all Potential Living Donors (PLDs) evaluated at a single centre over a 32-year period was conducted. Of the total cohort of 1208 PLDs, 298 were Accepted Living Donors (ALDs), resulting in 910 Failed Living Donors (FLDs). Data collected included donor demographics. In addition, in the ALD group, clinical and laboratory parameters at various points in donor follow-up, as well as mortality data was noted. In the FLD group reason for donor exclusion was documented.

Results

Of the 1208 PLDs, 697 (58%) were female. The majority (559; 46%) were of Black African descent, and related to the intended recipient (991; 82%).

Outcome of PLD evaluation varied significantly by race ($p<0.001$), with only a third of Black PLDs being accepted for donation. Black vs. Caucasian PLDs were more likely to fail work-up (52.1% vs. 39.3%; $p<0.001$) and be excluded for medical reasons (44% vs. 35%; $p<0.001$). Leading medical exclusions included hypertension, HIV and obesity.

In the ALD cohort, median follow-up time was 44 months (IQR 13.8 – 93.5 months). Hypertension was documented in 12.8% of ALDs at most recent follow-up compared to 4.7% of ALDs pre-donation ($p=0.06$). There was a significant increase in Albumin Excretion Rate (AER) following donation ($p<0.001$). There was a significant decline in the CKD-EPI eGFR between pre-donation (91.7 ± 19.1 ml /min/1.73 m^2) and the most recent visit post-donation (72.5 ± 20 ml/min/1.73 $m^{2;}$ $p<0.001$). 27% of ALDs had a CKD-EPI eGFR<60 ml/min/1.73 m^2 at most recent visit, however none required renal replacement therapy. There were 5 documented deaths, all unrelated to the development of renal dysfunction. Black ethnicity was not associated with increased risk of adverse outcome following donation.

Conclusions

There is a high exclusion rate for PLDs. Black PLDs are more likely to be excluded than Caucasian counterparts due to significant comorbidity. Although limited by high rates of

donors lost to follow-up, it is concerning that a quarter of ALDs developed an eGFR<60 ml/min/1.73 m^2 at last follow-up, with a significant increase in AER.

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ABBREVIATIONS / NOMENCLATURE

^{51}Cr-EDTA	Chromium-51-ethylene-diamine-tetra-acetic-acid
ACS	Acute coronary syndrome
AER	Albumin excretion rate
ALD	Accepted living donor
APOL1	Apolipoprotein L1
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CTA	Computed tomography angiogram
EBV	Epstein-Barr virus
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
FLD	Failed living donor
GFR	Glomerular filtration rate
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C antibody
HIV	Human immunodeficiency virus

HLA	Human Leukocyte Antigen
HR	Hazard ratio
IHD	Ischemic heart disease
IMA	Isolated medical abnormality
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
NSAIDs	Non-steroidal anti-inflammatory drugs
PLD	Potential living donor
PSA	Prostate-specific antigen
RLD	Related living donor
RRT	Renal replacement therapy
SA	South Africa
sCr	Serum creatinine
TB	Tuberculosis
UTIs	Urinary tract infections

CHAPTER 1: PROTOCOL AND EXTENTED REVIEW OF THE LITERATURE

1. BACKGROUND

1.1. Introduction

As the burden of end-stage kidney disease (ESKD) escalates globally, the growing demand for renal allografts cannot be met by deceased donors alone. [1, 2] This escalation is of particular concern in developing countries, as it is estimated that by the year 2030 in excess of 70% of patients with ESKD will reside in middle- and low-income countries, such as those in sub-Saharan Africa. [3, 4] Transplantation is the preferred modality of renal replacement therapy (RRT), having significantly better morbidity and mortality rates compared to long term dialysis. [5] Living donor transplants are known to offer improved allograft survival rates over deceased donor grafts. [5] In addition, living kidney donation offers the potential to significantly expand the kidney donor pool. [2] Rates of living kidney donation are increasing globally, with a twofold rise in the number of living donor transplants reported over the last decade in countries where registry data is available. [6]

Living donation necessitates healthy individuals to undergo major surgery without any direct self-benefit. [7] The advantages of living donor transplantation for the recipient must therefore be balanced against ensuring donor safety, both in the selection process of potential living donors (PLDs) and the post-donation care of accepted living donors (ALDs). [8-11]

To date, the outcome of living donation for donors has largely been assessed in the developed world. [6] Emerging studies now suggest that the risk of adverse outcomes amongst ALDs may have been underestimated. [12-14] There is a paucity of data amongst demographically diverse populations in the developing world. [15]

1.2. Physiology of uninephrectomy

Micro-puncture animal studies have informed much of what is understood about the pathophysiological sequelae of nephron mass reduction resulting from donor harvesting. [16, 17]

Uninephrectomy induces a series of both structural and functional adaptations at a glomerular level. [16] An increase in renal plasma flow in the remaining kidney results in sustained single nephron hyperfiltration, which is accompanied by a rise in intraglomerular pressure. [17] The release of various growth factors and cytokines mediates glomerular hypertrophy which is reflected by an increase in the renal volume. [16, 17]

These compensatory mechanisms facilitate the maintenance of a post-donation estimated filtration rate (eGFR) that is comparable to normal renal function, despite a loss of half the renal mass. [16] *Delanaye et al.* reported that the average post-donation eGFR reaches 65-70% of the pre-donation value (in donors ≤ 60 years of age) and that the progressive decline in eGFR following donation mirrors that which occurs with normal senescence. [18]

However, long-term sustained hyperfiltration may cause maladaptive alterations to remnant glomeruli which in turn lead to progressive renal injury. [16, 17] In animal models, hyperfiltrating glomeruli undergo morphological changes ultimately resulting in focal and segmental glomerulosclerosis. [17] This is postulated to be the pathophysiological mechanism accounting for the long-term complications arising post uninephrectomy, including the development of proteinuria, hypertension and progression to ESKD. [16]

A key consideration with regard to the animal model is that a 5/6 reduction in nephron mass of the experimental rat is not physiologically equivalent to a loss of half the nephron mass in an otherwise healthy individual. [19] A recent study by *Lenihan et al*. analysed glomerular dynamics following donation and suggested that single nephron hyperfiltration occurs largely independent of maladaptive glomerular hypertension. [20] This is thought to account for the observation that adverse renal outcomes occur relatively infrequently amongst living kidney donors. [21]

An additional concern is the adverse impact of nephron mass reduction on cardiovascular health. Numerous human studies have demonstrated an elevation in biomarkers associated with endothelial dysfunction and atherosclerosis following uninephrectomy. [22 – 25]

1.3. Clinical context

The practice of living kidney donation has evolved considerably since the first successful live donor transplant over sixty years ago. [26] Advances in therapy have led to renal

transplantation emerging as the preferred treatment modality for ESKD, with live donor pools accounting for a significant number of kidney transplants worldwide. [2, 6]

Living donation encompasses both related and unrelated donors. Unrelated donors may either be directed or purely altruistic. [11] Living donor paired exchanges and donor chains offer the potential to increase the utilisation of living donors in otherwise incompatible donor-recipient pairs. [27, 28]

As guided by the Kidney Disease Improving Global Outcomes (KDIGO) organization which developed an international standard of care for the live kidney donor, PLDs undergo an extensive multidisciplinary assessment prior to being accepted for living donation. [29] It is not uncommon for this rigorous work-up to detect occult disease in the prospective donor. [29] PLDs who are not accepted for donation are called failed living donors (FLDs). Multiple studies report similarly high rates of FLDs, ranging between 47-62%, with prospective Black donors most likely to be excluded. [30-34]

Regarding outcomes in ALDs, older data appeared to show no difference in the long-term medical outcomes in living kidney donors as compared to the general population with some studies even suggesting that kidney donors 'live longer'. [35, 36]. More recent studies, which have compared outcomes in ALDs to appropriately matched controls, have been less reassuring. [12-14] African-American donors were consistently under-represented in these studies, although the estimated risk of adverse outcome is believed to be highest in this population group. [15, 37, 38]

1.4. An overview of Failed Living Donors

Characterising the reasons for donor exclusion may identify modifiable factors that can be addressed in order to safely expand living donor pools. [33, 39]

1.4.1. Medical reasons for donor exclusion

Medical contraindications prevail universally as the most common reason for donor exclusion. [30-34]

Enhanced pre-donation screening highlights the declining health of the aging general population, as well as the growing burden of non-communicable disease globally. [4, 39, 40] It is estimated that roughly 10% of the world's population has chronic kidney disease (CKD), most of which is asymptomatic. [4, 41] Given this estimation, it can be extrapolated that roughly five million South Africans have underlying CKD. [42] Hypertension and diabetes constitute the main causes, mirroring global trends. [40, 42-44] Underlying both these disorders is the worldwide epidemic of obesity. The South African population's obesity rate is 49%, double the global rate. [44, 45] Numerous studies have found obesity, hypertension and diabetes to be the most prevalent medical reasons for potential donors failing to ultimately donate a kidney. [30-34]

In addition, sub-Saharan Africa has a high prevalence of human immunodeficiency virus (HIV). [4] The potential for donor exclusion due to communicable disease is therefore greater in this region. [4, 39, 42]

1.4.2. Non-medical reasons for donor exclusion

1.4.2.1. Immunological factors

ABO and cross-match incompatibility amongst donor-recipient pairs have historically been major limiting factors in living kidney donation. [30-32, 34]

Previously, immunological factors resulted in the exclusion of at least one-third of otherwise suitable donors. [46] In recent years, however, novel approaches have emerged to circumvent these immunological barriers. [47, 48] These include the use of immune modulatory therapy to allow HLA-desensitisation and ABO incompatible transplantation. [46-48] In addition, kidney exchange and domino-paired anonymous donation programs offer a cost effective alternative, without the added risk of complications arising from the use of additional intense immunosuppression needed to overcome immunological factors. [27, 48]

The outcomes of these strategies have thus far been reassuring, with similar graft survival rates being demonstrated as compared to standard living donor transplants. [27, 28, 46, 47] This further highlights their importance in sustaining an expansion in living donor pools. [48]

1.4.2.2. Psychosocial factors

All PLDs undergo mandatory evaluation to determine psychosocial suitability for donation. [39] During this process, motive for donation, socioeconomic support structures, and

general psychosocial wellbeing are assessed. [39] Aside from cultural factors, an increasingly common phenomenon is non-donation among medically suitable candidates who voluntarily withdraw from donation due to concerns regarding their prognosis following donation as well as fear of the potential complications of the surgical procedure itself. [30, 31, 33] Targeted donor education programs which can address such concerns early on in the evaluation process could potentially enhance living donor transplant rates by at least 10%. [33]

1.4.3. Outcome of donor evaluation by ethnicity

Weng et al. highlighted that Black (vs. non-Black) potential donors were more likely to be excluded for medical reasons, most notably hypertension and obesity. [34] Furthermore, a prospective cohort study determined the overall odds of donation to be 52% lower in African Americans as compared to Caucasians (OR 0.48; $p<0.001$), with similarly high rates of exclusion for diseases of lifestyle. [50]

African American donors are more likely to decide against donation. [33, 34, 50, 51] Reasons for this disparity in willingness to donate among African Americans were outlined in a study by *Purnell et al*. [52] Key issues highlighted include medical mistrust and cultural beliefs pertaining to bodily integrity. *Gill et al.* found socioeconomic inequality to be a significant barrier. [53] The incidence of living donation was lower amongst African American populations in the lowest income quintile (incidence rate ratio 0.84; 95% CI [0.78-0.90]).

In view of the above, various strategies have been proposed to enhance living donation rates in the African American population. [51, 54, 55] These include improved preventative medical care and educational programs to address unique concerns related to living donation in this subgroup. [51, 55]

1.5. An overview of Accepted Living Donors

1.5.1. A pre-2014 perspective

Older reports of long-term donor follow-up suggested that the risks of uninephrectomy were of limited clinical significance, with outcomes amongst living donors being comparable (if not superior) to that of the general population. [18, 35, 36, 58, 59, 64-66]

1.5.1.1. Renal outcomes

In a large longitudinal study by *Ibrahim et al.* 85% of a predominantly Caucasian cohort of donors were found to have a preserved GFR of greater than 60 ml/min/1.73 m^2 at a mean of 12 years following donation. [35] When compared to the general population, no additional risk of accelerated decline in GFR, hypertension or albuminuria was demonstrated post-donation. The incidence of ESKD was found to be significantly lower than that of the general American population, at a rate of 180 cases per million per year, as compared to 268 cases per million per year respectively ($p<0.001$). [35] These findings were consistent with numerous other studies that reported relatively benign renal outcomes following donation. [56-64]

1.5.1.2. Non-renal outcomes

A number of reports have compared long-term donor survival to population-based estimates. One such study by *Fehrman-Ekholm et al.* conducted over a 30-year follow up period found that donor longevity exceeded that of the general Swedish population, as survival rates were found to be superior in the donor group by 29% ($p<0.001$). [36] In addition, a Norwegian study reported that cardiovascular and overall mortality amongst donors were similar to demographically matched controls. [65] Major cardiovascular event rates were also found to be lower in donors compared to non-donors (2.8 vs. 4.1 events per 1000 person years, HR 0.66, 95% CI [0.48-0.90]). [66]

1.5.2. Critical analysis of pre-2014 data

Numerous concerns have been raised regarding study methodologies used in the reports prior to 2014, which favoured the interpretation of better outcomes amongst donors. [64, 67]

A primary concern has been that of selection bias generated by the use of the general population as a control group, as it represents a high risk comparator to live donors who are thoroughly screened and thus intrinsically healthier at baseline. [67] Additional concerns include the reliability of the data due to restrictive sample sizes, short follow-up durations and limited ethnic diversity amongst donor cohorts. [64, 67]

These shortcomings underscore the need to undertake studies that determine attributable risk by comparing donors to appropriate controls, namely matched, healthy non-donor population groups with large cohort numbers and long duration of follow-up. [68]

1.5.3. Current data on living donation

Few studies have compared long-term outcomes between donors and healthy matched non-donors. These studies highlight evolving concerns pertaining to morbidity and mortality following kidney donation. [68] Moreover, emerging prospective data on long-term donor follow-up has provided valuable new insight into donor nephrectomy outcomes. [69]

1.5.3.1. Renal outcomes

In the first prospective study conducted on living donors to date, *Janki et al.* assessed 100 donors over a median follow-up time of 10 years at two Dutch transplant centres. [70] There was a significant decline in the eGFR of 12.9 ml/min/1.73 m^2 ($p<0.001$) at follow-up. One-fifth of the cohort had an eGFR between 30-60 ml/min/1.73 m^2 at the study end-point. [70] In a report subsequently published by the same primary investigator, variables associated with an accelerated decline in renal function following donation were evaluated in a prospective cohort of 190 donors. [71] Over a 5-year follow-up period, a 33.6% decline in mean eGFR was noted following donor nephrectomy, with longitudinal analysis revealing a lower eGFR among male donors and older age ($p<0.001$). In this cohort, renal function had stabilized after an expected initial decrement immediately following nephrectomy and no donor required the institution of RRT.

Conversely, two reports suggest that living donors are at increased risk of developing ESKD as compared to matched controls. *Mjøen et al.* studied a large cohort of Caucasian living donors in Norway and found an eleven-fold increase in the relative risk of ESKD after donor nephrectomy. [12] The second, a US-based study by *Muzalle et al.* included 96214 donors with a median follow-up of 8 years. [14] Here, the estimated risk of ESKD was found to be 7.9-fold higher in living donors. Importantly however, the absolute 15-year incidence of ESKD in both these studies remained low at less than 1%. [68]

Although an uncommon occurrence, prior living donors who require RRT have favourable post-transplant outcomes, particularly in the US where waiting times for kidney transplant are brief as national policy allocates priority to these patients. [72] Event rates for acute dialysis following donation are also low. [60, 73]

1.5.3.2. Donor Mortality

In a retrospective cohort, *Mjøen et al.* showed that all-cause mortality in the first decade following donation remained comparable to healthy matched non-donor groups. [12] However, at 25 years, survival curves diverged, with the cumulative all-cause mortality increasing by 5% amongst donors. Over a median follow-up of fifteen years, the same study also found an increased risk of cardiovascular mortality amongst donors (HR 1.4; $p<0.001$). In contrast, prospective studies by *Janki et al.* report reassuring donor survival over mean follow-up periods of between 5 and 10 years, with mortality being due to causes unrelated to donation. [70, 71]

1.5.4. Medically complex donors

Critical organ shortages have led to the emergence of expanded criteria for donor eligibility, in order to augment living donor pools. [74]

Previously published data reported uncertainty in the long-term outcomes of donors with preceding isolated medical abnormalities (IMAs), including those who were older (≥ 65 years of age) or had pre-existing risk factors for CKD such as obesity (BMI 30-35 kg/m^2) and pre-existing hypertension (stage 1 controlled on a single agent with no end-organ damage). [75] However, recent literature in this regard has largely been reassuring. A 2014 systematic review including studies using appropriately matched cohorts reported favourable outcomes with the use of older donors (up to the age of 70), as well as obese donors (irrespective of body mass index). [74] Despite concerns around a greater degree of pre-existing glomerulopaenia in hypertensive donors, outcomes in this subgroup have been comparable to that of normotensive donors. [71, 76-79]

These findings are supported physiologically by the demonstration of similar compensatory changes in the remaining kidney of medically complex donors as compared to standard donors. [80]

1.5.5. Effect of race on donor outcome

Comparative studies are limited but have highlighted that Black donors have an increased risk of adverse post-donation outcomes as compared to Caucasian donors. [15, 37, 38, 59]

Over a median follow-up of 6.3 years, the risk of peri-operative mortality was reported to be threefold greater amongst Black donors. [64] Following donation, the all cause risk of re-hospitalisation also greater amongst this subgroup (HR 2.6, 95% CI [1.54-3.03]). [81] There was however no statistically significant cause to account for these findings among black donors. [64, 81]

At 7 year follow-up, the incidence of renal disease, including proteinuria and nephrotic syndrome, was higher amongst black donors as compared to Caucasian counterparts. [38] *Lentine et al.* showed that Black donors have a greater post-nephrectomy risk of developing hypertension (HR 1.52; 95% CI [1.23-1.88]) and diabetes (HR 2.31; 95% CI [1.33-3.62]). [15] In addition, Black donors were twice as likely to develop CKD. [15] The absolute risk of ESKD has consistently been shown to be greater in Black donors. [14, 59]

A study of donation patterns revealed that Black donors are more likely to be related to the recipient than Caucasian donors (88% vs. 74%; p=0.007). [82] Genetic factors, including the identification of coding variants in the Apolipoprotein L1 (APOL1) gene, are thought to underlie the elevated risk for adverse renal outcomes amongst Black patients, although this association is yet to be proven amongst Black living kidney donors. [83-87]

1.5.6. Donor ESKD risk projection

In order to inform donor counselling and selection, various models have been developed to estimate the projected long-term risk of ESKD following uninephrectomy. [13, 88-91]

The first extrapolated data is from the *Mjøen et al.* cohort of 1901 Caucasian donors. [12] In this model, with the assumption that all donors live to 80 years of age and that the incidence of ESKD remains constant with time, the estimated risk of a 60-year old PLD developing ESKD is predicted to be 1 in 150. With a younger age at donation, the estimated risk of ESKD incrementally increases, being 1 in 75 for a 40-year old PLD, and 1 in 50 in a 20-year old PLD. [13] Furthermore, a risk calculator developed by *Ibrahim et al.* to assess renal outcomes that portend ESKD in Caucasian donors found that the development of post-donation diabetes and hypertension was associated with a two-fold higher risk of ESKD. [88]

The only model that included risk projection amongst racially diverse donors was generated using US population based data. [89] In this report, the projected risk of ESKD amongst PLDs over a 15-year time period was found to be 3.5 - 5.3 times greater than the projected risk in the absence of donation. Furthermore, the risk of ESKD was identified as being highest amongst young Black PLDs – an average 40 year old Black donor had a 3.9 times higher 15-year risk of developing ESKD as compared to a Caucasian donor of the same age and baseline characteristics. [89]

Recent studies highlight a strong genetic component to the ESKD risk profile in living kidney donors; donors who are first-degree relatives to the recipient have consistently been shown to have a significantly greater predicted risk for ESKD following donation. [90, 91]

1.5.7. Measurement of renal outcomes post donation: eGFR

Post uninephrectomy, the assessment of renal function in donors requires a reliable method for the determination of GFR. This allows for the timeous identification of a possible decline in renal function following donation. [92, 93]

Ideally, GFR should be accurately measured in donors as concerns have been expressed regarding the use of creatinine-based equations to estimate renal function in individuals with a single kidney. [93] In practise however, calculated estimates of GFR are cost effective, and are therefore of particular relevance in resource limited settings. [92] Although many studies have applied the Cockroft-Gault or Modification of Diet in Renal Diseases formulas, the estimate now recommended for use in the assessment of renal function in living donors following uninephrectomy is the Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation. [92,93] This formula has been shown to closely approximate measured GFRs in living donors and has superior precision and accuracy as compared to other creatinine-based equations. [94]

1.5.8. Donor follow-up

The need for structured donor follow-up is critical – particularly in an era where medically complex donors are frequently utilised and longitudinal data reveal a risk of comorbidity following donation. [74, 95] Monitoring of donors facilitates the early diagnosis and timeous institution of therapy where indicated, thus minimising the risk of potential complications. [96] Nevertheless, donor follow-up rates remain universally low. [97-99] In a 2015 report, *Keshvani et al.* noted that, by two years following donation, 40% of all transplant centres

lose contact with more than two-thirds of their donors. [100] This underscores the likelihood that potential adverse donor outcomes are substantially underreported. [67]

1.5.8.1. Barriers to donor follow-up

Incomplete donor follow-up can be attributed to both donor and transplant centre factors. [100, 101] *Schold et al.* highlighted that younger age at donation, Black race, poor health literacy and distance of domicile in relation to follow-up centre were all independent risk factors for low follow-up rates. [101] This is consistent with *Weng et al.'s* report which identified similar risk factors. [102] *Weng et al.* also noted that amongst donors who had pursued follow-up, only 8% had been assessed by a nephrologist following donation. [102] In addition, higher rates of donor defaulting are reported amongst transplant centres with a higher volume of living donor transplants per year, as well as those with limited resources to trace patients following donation. [101]

1.5.8.2. Improving donor follow-up

The institution of targeted strategies to augment donor follow-up has led to improved donor compliance at many transplant centres. [100-103] In the *Keshvani et al.* cohort, increased efforts to telephonically contact donors for follow-up, patient education classes conducted by a dedicated transplant nurse as well as reimbursement of donors for transport costs incurred by follow-up visits were all shown to significantly improve donor follow-up at 2 years ($p<0.001$). [100] Dedicated initiatives to improve follow-up in particular at-risk

subgroups such as younger donors and those with lower educational attainment have also been of benefit. [101]

1.6. The South African context

The lack of access to RRT in developing countries has been well documented. [4] In South Africa (SA), the burgeoning HIV/AIDS epidemic has demanded a disproportionate quantum of healthcare resources, further limiting the provision of RRT. [44,104,105] As a result, a significant number of South Africans are at risk of premature death due to ESKD. [3]

Living kidney donation thus offers a cost-effective measurement to facilitate definitive RRT in the South African setting. [104] Living donor transplant rates are however low across many centres in SA, with only 93 performed in the year 2014 despite the rapidly growing demand for donor organs. [104,105] Of further concern is that the risks associated with living donation have historically been poorly defined in demographically diverse populations. [15]

To date, only four studies relating to living kidney donation in South Africa have been undertaken. The first, conducted in Johannesburg in 1986 by *O' Donnell et al*. studied 33 living related donors over a mean follow-up period of 5.8 years. [106] Donors were found to have substantial rise in diastolic blood pressure ($p<0.001$), as well as inclination towards a significant decline in creatinine clearance following donation (p 0.0558). In a series by *Naicker et al.* 135 related living donors were reviewed over a ten year period. [107] The

majority of donors in this cohort were female (63%) and of Indian origin (58%), with a mean age of 34 years. Here, blood pressure post nephrectomy remained essentially unchanged, although three donors demonstrated clinically significant proteinuria following donation. The post-donation serum creatinine was found to be within normal limits, despite a mean rise of 33.4% over the follow-up period. The findings of the third study by *Abdu et al*. highlighted the need to encourage living donation and facilitate donor follow-up, which was noted to be poor in roughly 40% of the cohort. [108] The final report described reasons for donor exclusion in 117 prospective donors at a Cape Town centre. [109] In this study, only 17% of donors ultimately donated, with the remainder excluded for predominantly immunological and medical reasons such as obesity, hypertension and CKD.

1.7. Summary

Living kidney donation has emerged as the preferred strategy to ameliorate the growing demand for renal allografts worldwide. [6] It is thus essential that the transplant community investigates methods to sustain living donor pools without compromising donor safety. [29, 39] This is particularly relevant as recent data highlights a substantial risk for adverse outcomes amongst prior living donors, although outcomes in racially diverse populations have been poorly characterised. [15, 35, 36] In order to tailor the informed consent process, attention to long-term outcomes amongst diverse living kidney donors is needed. [37, 67]

The present study was undertaken in an effort to evaluate living kidney donation in the South African context with a view to identifying reasons for donor exclusion which may in

future facilitate the assessment of potentially modifiable barriers to donation, and in an attempt to characterise long-term morbidity and mortality following donation which may better inform the consent process for prospective donors in this setting.

2. OBJECTIVES

2.1. Primary Objective

- To determine donor morbidity and mortality after donation.
- Analysis of morbidity will focus on the development of
    a. New onset hypertension following donation (BP ≥140/90)
    b. Chronic kidney disease following donation, defined as the development of either of the following
        i. New onset proteinuria (AER >300mg/day)
        ii. An eGFR <60 ml/min/1.73 m^2 (using the CKD-EPI formula)

2.2. Secondary Objectives

- To determine the reasons for exclusion of potential donors from living kidney donation
- To determine the prevalence of ESKD following donation (eGFR <15 ml/min/1.73 m^2 using the CKD-EPI formula)
- To determine potential risk factors associated with proteinuria and/or a reduced eGFR post kidney donation, by evaluating –
    a. donor demographics
    b. the presence of isolated medical abnormalities prior to donation, defined by:
        - a borderline pre-donation ^{51}Cr-EDTA GFR (<80 ml/min/1.73 m^2)
        - pre-existing hypertension (well controlled on a single agent with no end-organ damage)
        - class I obesity (BMI 30-35 kg/m^2)
- To determine the proportion of patients lost to follow-up post donation

3. METHODOLOGY

3.1. Study design

A single centre retrospective observational study will be conducted of all patients attending the Living Donor Clinic in the Renal Unit at CMJAH over a 32-year period between 01 January 1983 and 31 July 2015. The closing date for sampling reflects the period of protocol submission for this study.

The cohort will be comprised of 1208 potential living donors, of which:

- 910 are failed living donors, assessed between 01 January 1990 and 31 July 2015
- 298 are accepted living donors, assessed between 01 January 1983 and 31 July 2015

3.2 Data collection

3.2.1 Data collection for failed living donors

Data collection for failed living donors will comprise the following parameters:

- Demographic data – age at assessment, gender and ethnicity
- Family history of the donor
- Relation to the intended recipient – whether related, unrelated or altruistic
- The outcome of eligibility evaluation

- If excluded from living donation, reasons for non-donation will be documented, which will be categorised as:
  - donor-recipient related,
  - donor-related,
  - recipient-related, or
  - miscellaneous.
- The indications and findings of any renal biopsy undertaken on a donor will be recorded

3.2.2 Data collection for accepted living donors

Data collection for accepted living donors will comprise the following parameters:

- Demographic information – gender, ethnicity, age at donation (as well as age at each follow-up point)
- Family history of the accepted donor
- Details pertaining to the donation, specifically:
  - relation to the recipient, as well as cause of renal failure in the recipient
  - the date of donation
  - the graft outcome (if known)
- The last follow-up date at the Living Donor Clinic and the approximate number of post-donation follow-up visits
- Domicile in relation to the Living Donor Clinic (in kilometres from transplant centre)
- The reason for lost to follow-up (if known)
- Baseline characteristics at donation, including:

  - Body mass index
  - Urine albumin : creatinine ratio
  - Systolic blood pressure
  - Diastolic blood pressure
  - Baseline serum creatinine
  - eGFR as defined by an isotope study, the chromium-51-ethylene-diamine-tetra-aceticacid scan (^{51}Cr EDTA scan) as well as the CKD-EPI formula
  - Habits, including smoking status and history of alcohol consumption
  - History of pre-existing medical condition(s)
- Characteristics at follow-up (correlated with time after donation), including:
  - Body mass index
  - Urine albumin : creatinine ratio
  - Systolic blood pressure
  - Diastolic blood pressure
  - Serum creatinine
  - eGFR as defined by the CKD-EPI formula
  - Habits, including smoking status and alcohol consumption
  - Development of co-morbid disease
  - History of nephrotoxic drug intake

The above variables will be retrospectively collected from data recorded at the patients' first follow-up visit post-donation, one-year post-donation visit, and at the most recent follow-up visit.

- Mortality data will be collected in accepted living donors that demised during the study period, and will include:
  - age at death
  - the time from donation to mortality
  - cause of death, whether related to renal disease, a cardiovascular event or other cause

3.3 Definition of variables

3.3.1 Classification of donors

- Potential living donors (PLDs) – refer to all donors assessed at the CMJAH Living Donor Clinic
- Failed living donors (FLDs) – refer to the sub-group of PLDs excluded from living kidney donation
- Accepted living donors (ALDs) – refer to the subgroup of PLDs that ultimately donated a kidney

3.3.2 Hypertension

Defined as per the Eighth Joint National Committee (JNC8) guidelines for blood pressure targets:

- For donors with a current age of more than sixty years:
  - a systolic blood pressure of more than 150mmHg, with
  - a diastolic blood pressure of more than 90mmHg
- For donors with a current age of less than sixty years:
  - a systolic blood pressure of more than 140mmHg, with
  - a diastolic blood pressure of more than 90mmHg

3.3.3 Albuminuria

Quantified as per the revised Kidney Disease Improving Global Outcomes (KDIGO) chronic kidney disease classification into three stages of albuminuria based on the albumin excretion rate (AER) in milligrams per day (mg/day):

- A1: Normal or mildly increased (AER <30 mg/day)
- A2: Moderately increased (AER between 30 - 300 mg/day)
- A3: Severely increased (AER >300 mg/day, with nephrotic range proteinuria defined as >3500 mg/day)

3.3.4 Glomerular filtration rate

- Pre-donation GFR will be defined:
  - as per isotope study: ^{51}Cr EDTA scan
  - as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, expressed as:

GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

where: **GFR** = glomerular filtration rate in ml/min/1,73m^2

S_{cr} = serum creatinine in mg/dL

κ = 0.7 for females and 0.9 for males

α = -0.329 for females and -0.411 for males

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

- Post-donation GFR will be calculated by the CKD-EPI formula, as expressed above.

3.3.5 Chronic kidney disease

Defined as per the revised Kidney Disease Outcomes Quality Initiative (KDOQI) as either kidney damage or GFR<60 ml/min/1.73 m^2 for ≥ 3 months. Kidney damage encompasses pathological abnormalities or markers of damage, including biochemical or radiological abnormalities. GFR is further classified into stages (table 1.1).

Table 1.1 | Revised KDOQI classification for chronic kidney disease

GFR Stages	GFR (ml/min/1,73 m^2)	Classification
1	>90	Normal
2	60 – 89	Mildly decreased
3a	45 – 59	Mildly to moderately decreased
3b	30 – 44	Moderately to severely decreased
4	15 – 29	Severely decreased
5	<15	ESKD

3.3.6 Body mass index

- BMI will be calculated as weight (in kilograms) divided by height (in meters) squared.
- It will then be sub-classified as per the World Health Organisation (WHO) international BMI classification (table 1.2).

Table 1.2 | WHO international classification of BMI

Classification	**BMI (kg/m^2)**
Underweight	< 18.5
Normal Range	18.5 to 24.99
Overweight	≥ 25
Pre-obese	25 to 29.99
Obese	≥ 30
- Obese Class I	30 to 34.99
- Obese Class II	35 to 39.99
- Obese Class III	≥ 40

3.3.7 Isolated medical abnormalities

Refers to donors with any of the following characteristics prior to donation:

- A borderline ^{51}Cr-EDTA GFR <80 ml/min/1.73 m^2
- Pre-existing hypertension well-controlled on a single agent with no end-organ damage
- Class I obesity (BMI 30 - 35 kg/m^2)

4. STATISTICAL ANALYSIS

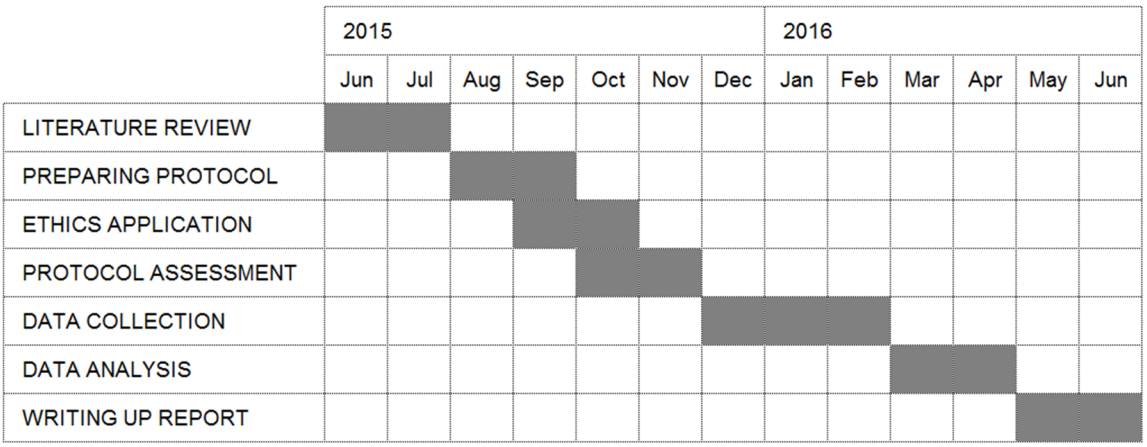
- Data analysis will be conducted using STATISTICA 12, a software package developed by *StatSoft*
- All data will be tabulated in a *Microsoft Excel* spreadsheet
- The distribution of continuous variables will be analysed using the Shapiro Wilk W test and by visual inspection of the histogram plot. The central measurement will be indicated by the mean for normally distributed variables and by the median for non-parametric data; dispersion will be presented as standard deviation and interquartile range, respectively.
- The categorical variables will be presented as percentages
- Statistical comparisons will be performed with the Student's t-test for continuous normally distributed variables and the chi-squared test for categorical variables. Where appropriate, the one-way ANOVA and Wilcoxon matched pairs testing will be applied.
- For the accepted donor cohort, a multiple linear regression analysis will be performed to identify independent factors associated with a reduced eGFR of <60 ml/min/1.73 m^2 at last follow-up.
- The Cox proportional hazard model will be applied to assess variables which impact on donor follow-up. If last follow-up is more than six months before the study end-point, donor defaulting will be assumed.
- A p-value of less than 0.05 will be considered to indicate statistical significance.

5. ETHICS

- Permission for this study was obtained from the Human Research Ethics Committee (Medical) – Clearance Certificate Number: M150923 (Chapter 3 – Appendix B). Permission to access patient records was obtained from the Head of Nephrology at CMJAH, as well as the Clinical Director and CEO of the institution.
- Patient confidentiality will be maintained by randomly allocating each patient record to a study number, allowing patient data to be kept strictly anonymous. All collected data and inferences thereof will then be analysed collectively.

6. TIMING

Gantt chart showing the timeline of the study:



7. FUNDING

All funding for this study will be borne by the author.

8. POTENTIAL LIMITATIONS

- Information bias may occur as a result of poor record keeping or incomplete data in the records
- Patients lost to follow-up may underpower the capacity of the study to assess certain outcomes

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CHAPTER 2: PROPOSED MANUSCRIPT

Living kidney donation in a developing country

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ABSTRACT

Living kidney donation is increasing in global significance as the preferred therapeutic modality to ameliorate the widening demand for renal allografts. There is limited data evaluating living donation in developing countries. We assessed reasons for non-donation and outcomes following donation amongst a cohort of 1208 ethnically diverse potential living donors over a 32-year period at a transplant centre in South Africa. Medical contraindications were the commonest reason for donor exclusion. These included hypertension, human immunodeficiency virus and obesity. Black donors were more likely to be excluded from donation (52.1% vs. 39.3%; $p<0.001$) particularly for medical reasons (44% vs. 35%; $p<0.001$). Amongst 298 accepted live donors, estimated glomerular filtration rate dropped below 60 ml/min/1.73m^2 in 27% of patients at median follow-up of 3.7 years, although none required the initiation of renal replacement therapy. Following nephrectomy, severely increased albuminuria of >300 mg/day was noted in 4% of donors and 12.8% developed new-onset hypertension. Five donors demised of causes unrelated to renal outcomes. Black ethnicity was not associated with an increased risk of adverse post-donation outcome. This study shows a

substantial donor exclusion rate with considerable racial variation in the outcome of donor evaluation. A proportion of donors demonstrated a significant decline in renal function following nephrectomy, highlighting the need for close long-term donor follow-up.
KEYWORDS: living kidney donation, developing country, potential living donors, donor exclusion, donor outcomes

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INTRODUCTION

The prevalence of end-stage kidney disease (ESKD) continues to rise globally[1] and contributes significantly to the burden of chronic disease in developing countries.[2] It is estimated that by the year 2030, in excess of 70% of patients with ESKD will reside in middle and low income countries, such as those in sub-Saharan Africa.[3] Historically, renal replacement therapy (RRT) has been limited in these settings, with access being lowest in Africa, where less than one-fifth of individuals needing RRT receive it.[4]

South Africa faces a unique set of challenges in addressing this RRT gap.[5] With the rising scourge of communicable diseases including human immunodeficiency virus (HIV) and tuberculosis demanding a disproportionate quantum of healthcare resources,[6] the provision of expensive therapies such as RRT has the potential to exert significant strain on its emerging

economy.[7] Due to pre-existing disparities in the provision of renal care, RRT in South Africa is at present largely concentrated in the privately funded sector; [8-10] whilst in the state sector, which serves more than 80% of the population, dialysis treatment is rationed with only those patients who are eligible for renal transplant being accepted. [7, 9] The present national transplant rate of 4.6 per million population in South Africa is on a downward trend,[8] well below the transplant rates of other middle income countries.[2, 8, 11] Without emergent intervention to expand the availability of transplantation in the South African population, already strained dialysis programs are at risk of collapse.[7] The majority of renal transplants in the local state sector program are from deceased donors; living donation, whether altruistic or donor-directed, offers a mechanism to increase transplantation rates.

Indeed, living kidney donation has been shown to be a cost-effective therapeutic modality to ameliorate the growing demand for sustainable RRT in the developing world.[1, 2, 9, 12] Living donation does, however, require that healthy individuals endure a major surgical procedure devoid of any direct self-benefit.[12] The numerous advantages of pre-emptive transplantation for the recipient must therefore be carefully balanced against maintaining immediate and long-term donor safety.[13-16]

Data suggests that up to two-thirds of potential living donors fail to complete the donation process.[17-21] Understanding the reasons for non-donation is required to identify possible modifiable barriers for intervention in order to augment living donation rates.[17,20] Furthermore, obtaining informed consent for donation is a challenge as consensus regarding the risks to the accepted donor following nephrectomy remain unclear,[22] particularly amongst donors of black ethnicity who seem to bear the greatest risk of adverse outcomes.[23-26] Older reports of

long-term donor follow-up suggested that the risks of uninephrectomy were of limited clinical significance, with donor outcomes largely comparable to that of the general population.[27-30] In contrast, emerging data, with appropriately matched control groups, highlight poorer long term survival and an elevated risk of ESKD amongst living donor cohorts. [31-33]

There is a paucity of data on the living donor selection process and outcomes at post-donation follow-up amongst demographically diverse populations in the developing world. The present study was undertaken to evaluate living donation in the South African context. The aim was to characterise reasons for non-donation, examine morbidity and mortality following donation, and to identify if any differences exist in outcomes among demographic subgroups in this setting.

RESULTS

Between January 1983 and July 2015, 1208 potential living donors were assessed at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a transplant centre in South Africa. Only a quarter (n=298) of assessed patients were accepted for living donation, resulting in 910 failed living donors (FLDs).

The demographic characteristics of the potential donor population are presented in Table 2.1. The most represented age group was that of 30-39 years (428; 35.4%). The majority of potential donors were female (697; 58%), of Black African descent (559; 46%) and biologically related to the intended or eventual recipient (991; 82%).

Medical contraindications to donation were the most common cause for donor disqualification (363; 39.9%); of which obesity, hypertension and HIV were most prevalent. Immunological barriers resulted in the exclusion of a further 19% of potential donors (n=173). A significant proportion (222; 25%) of donors were medically suitable but ultimately did not proceed to donation. This subgroup encompassed exclusions for recipient-related factors (120; 13.2%) and prospective donors who voluntarily withdrew from donation due to lack of further interest (102; 11.2%). Eighty-five (9.3%) of referred donors were lost to follow-up during the process of evaluation (Table 2.2).

Outcome of donor evaluation varied significantly by race (Table 2.3). Black donors were more likely to fail work-up (51.2% vs. 39.3%; $p<0.001$) and be excluded for medical reasons (44% vs. 35%; $p<0.001$). In addition, forty-eight (49.5%) of medically suitable donors who voluntarily withdrew were of Black ethnicity.

Median follow-up of the accepted donors was 3.7 years after donation (IQR 1.2-7.8 years). Clinical and laboratory parameters for this subgroup at baseline and at three successive post-donation follow-up points (at first visit, at one-year and at most recent visit) are shown in Table 2.4. Thirty-eight donors (12.8%) developed hypertension at follow-up, although the frequency of new-onset hypertension was not significantly different as compared to baseline ($p=0.06$). Statistically significant increase in both systolic and diastolic blood pressure was detected at one-year follow-up ($p<0.001$). There was a significant increase in albuminuria over time between the pre-donation and post-donation (most recent visit) ($p<0.001$), however the albumin excretion rate (AER) remained within normal limits. Thirteen donors (4%) developed

the primary endpoint of AER>300 mg/day, one of which was a living-unrelated donor that developed biopsy-proven membranous glomerulonephritis following donation.

At most recent follow-up, estimated glomerular filtration rate (eGFR), determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, was significantly lower compared to baseline measurements (72.5 vs. 91.7 ml/min/1.73 m^2 respectively, $p<0.001$), representing a decrease in GFR of 21%. Eighty accepted donors (27%) developed a CKD-EPI-eGFR of less than 60 ml/min/1.73 m^2 at most recent follow-up. Regression analysis identified multiple risk factors associated with this outcome (Table 2.5). These included Caucasian ethnicity, a lower eGFR at baseline and preceding visits, and an elevated blood pressure at the one year visit. However, none of the donors developed ESKD or required the institution of RRT.

Black African ethnicity did not portend an increased risk of adverse outcome at most recent follow-up (Table 2.6). Over a longer median follow-up duration post donation, Black donors had better serum creatinine levels and calculated eGFR. However, donors of Black African origin had higher mean systolic blood pressures at last follow-up, although still within normal limits.

Sixty-seven donors (22.5%) had an isolated medical abnormality (IMA) prior to donation. This subgroup included donors with a pre-donation body mass index (BMI) of between 30-35 kg/m^2 (n=32); donors with a baseline isotope GFR of less than 80 ml/min/1.73 m^2 (n=21) and those with pre-existing hypertension, well controlled on a single agent with no end-organ damage (n=14). A third of donors with an IMA were of Black African ethnicity. Class I obesity at baseline was not associated with an increased risk of developing hypertension ($p=0.09$) or an eGFR of

less than 60 ml/min/1.73 m^2 (p=0.71) at follow-up. A pre-donation isotope GFR of less than 80 ml/min/1.73 m^2 was associated with an eGFR less than 60 ml/min/1.73 m^2 at most recent follow-up (p=0.02); the incidence of new onset hypertension was not significantly greater in this subgroup (p=0.27).

With respect to non-renal outcomes, in the perioperative period sixteen donors (5.4%) suffered from complications including an iatrogenic pneumothorax (n=1); hospital acquired infections (n=3); and prolonged pain at the site of the nephrectomy scar (n=11). During the study period there were a total of 5 deaths (1.7%), one of which occurred in the immediate post-operative period. The remaining four deaths resulted from trauma and were thus unrelated to donation. Four donors (1.3%) required psychological support for major depressive disorder (n=2) and substance abuse (n=2).

Caucasian donors were more likely to default follow-up (Table 2.7). Donors who resided more than 100 kilometres from the transplant centre had significantly shorter durations of post-donation follow-up. In addition, all donors aged 18-21 years (n=9) at the time of donation were lost to follow-up; donors over the age of twenty-one were at significantly lower risk of defaulting follow-up. Gender and degree of relationship to the recipient were not associated with poorer follow-up.

Table 2.1 | Donor demographics

Characteristic	Donors excluded n=910 (75.3%)	Donors accepted n=298 (24.7%)	Total evaluated n=1208
Age (in years)			
18-21	54 (5.9) [a]	9 (3.0)	63 (5.2)
22-29	213 (23.4)	71 (23.8)	284 (23.5)
30-39	315 (34.6)	113 (37.9)	428 (35.4)
40-49	221 (24.2)	85 (28.5)	306 (25.3)
50-59	93 (10.2)	19 (6.4)	112 (9.3)
≥60	14 (1.53)	1 (0.3)	15 (1.2)
Gender			
Female	522 (57.4)	175 (58.7)	697 (57.7)
Male	388 (42.6)	123 (41.3)	511 (42.3)
Ethnicity			
Black	474 (52.1)	85 (28.5)	559 (46.2)
Caucasian	358 (39.3)	175 (58.7)	533 (44.1)
Indian/Asian	38 (4.2)	26 (8.7)	64 (5.3)
Coloured	40 (4.4)	12 (4.1)	52 (4.3)
Relation to recipient			
Biological	722 (79.0)	269 (90.3)	991 (82)
First degree relative	631 (69.0)	256 (85.9)	887 (73.4)
Other relative	91 (10.0)	13 (4.7)	104 (8.6)
Non-biological	188 (21.0)	29 (9.73)	217 (18.0)
Directed	180 (19.7)	29 (9.73)	209 (17.3)
Non-directed	8 (0.9)	0	8 (0.7)

[a] Values are expressed as n (%)

Table 2.2 | Reasons for non-donation

			n	%	n	%
DONOR RELATED FACTORS	MEDICAL	Hypertension	90	9.9	363	39.9
		Human Immunodeficiency Virus	45	4.9		
		Obese class I (BMI 30-34)	40	4.4		
		Obese class II (BMI 35-39)	40	4.4		
		Chronic kidney disease (eGFR <70)	37	4.1		
		Hypertension and obesity	29	3.2		
		Obese class III (BMI ≥40)	9	1		
		Persistent iron deficiency anaemia	8	0.9		
		Diabetes	5	0.5		
		Persistent microalbuminuria	5	0.5		
		Hepatitis B	5	0.5		
		Hepatitis C	5	0.5		
		Hypertension and chronic kidney disease	4	0.4		
		Metabolic syndrome	4	0.4		
		Recurrent urinary tract infections	4	0.4		
		Tuberculosis	4	0.4		
		Familial hypercholesterolemia with atherosclerosis	3	0.3		
		Ischaemic heart disease	2	0.2		
		Valvular heart disease	2	0.2		
		Chronic obstructive pulmonary disease	2	0.2		
		Poorly controlled epilepsy	2	0.2		
		Von Willebrand Disease	2	0.2		
		Primary hyperparathyroidism	2	0.2		
		Systemic lupus erythematosus	2	0.2		
		Syphilis	2	0.2		
		Glomerulonephritis	1	0.1		
		Autosomal dominant polycystic kidney disease	1	0.1		
		Alport syndrome	1	0.1		
		Hashimoto's thyroiditis	1	0.1		
		Grave's disease	1	0.1		
		Ankylosing spondylitis	1	0.1		
		Incidental malignancy	1	0.1		
	UROLOGICAL	Nephrolithiasis	6	0.6	8	0.9
		Obstructive uropathy	2	0.2		
	ANATOMICAL	Multiple renal arteries bilaterally	14	1.5	28	3.1
		Congenital renal anomaly	8	0.8		
		Fibromuscular dysplasia	5	0.5		
		Renal artery stenosis	1	0.1		
	PSYCHOSOCIAL	Withdrew voluntarily	102	11.2	208	22.9
		Lost to follow-up	85	9.3		
		Psychiatric disorder	14	1.5		
		Polysubstance abuse	7	0.8		
RECIPIENT RELATED FACTORS		Transplant candidate demised	47	5.2	120	13.2
		Alternate donation received (from alternate living donor)	32	3.5		
		Transplant candidate became medically ineligible	21	2.3		
		Alternate donation received (from deceased donor)	20	2.2		
DONOR-RECIPIENT RELATED FACTORS		ABO incompatibility	96	10.5	173	19
		Positive cytotoxic antibody cross-match	77	8.5		
MISCELLANEOUS		Other[a]	10	1.1	10	1.1

Abbreviations: BMI, Body mass index; eGFR, estimated glomerular filtration rate

[a] Includes donors disqualified for age >70 years, pregnancy and incarceration

Table 2.3 | Donor exclusion stratified by ethnicity

	Caucasian	Black	p-value
Donor-related factors			
Medical	125 (34.9) [a]	210 (44.3)	<0.001
Urological	6 (1.7)	1 (0.2)	<0.001
Anatomical	23 (6.4)	5 (1.1)	<0.001
Psychosocial	77 (21.5)	109 (23.0)	<0.001
Donor-recipient related factors			
Immunological	70 (19.6)	95 (20.0)	<0.001

[a] Values are expressed as n (%)

Table 2.4 | Comparative clinical parameters in accepted living donors

	Pre-donation	Post-donation			p-value
		First Visit	One Year Visit	Most Recent Visit	
Systolic BP (mmHg) [a]	119 (11.8)	121 (17.3)	126 (17.1)	125 (16.0)	<0.001 [c]
Diastolic BP (mmHg) [a]	73 (9.1)	75 (11.7)	78 (12.9)	79 (10.7)	<0.001 [c]
Albuminuria (AER in mg/day) [b]	6 (3-12)	10 (3-28)	13 (3-77)	7 (3-29)	<0.001
Serum Creatinine (µmol/L) [a]	85 (14.6)	114 (21.0)	104 (15.7)	103 (24.3)	<0.001
CKD-EPI eGFR (ml/min/1.73m^2)[a]	91.7 (19.1)	70.6 (19.4)	86.1 (19.7)	72.5 (20.0)	<0.001

Abbreviations: BP, blood pressure; AER, albumin excretion rate; CKD-EPI eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation

[a] Values are mean (± SD)

[b] Values are median (± IQR)

[c] Applies to analysis commencing at one-year follow-up

Table 2.5 | Logistic regression analysis of variables associated with an eGFR<60 ml/min/1.73m^2 at most recent follow-up

	Coefficient	Wald test	p-value
Age at donation	-0.023	0.11	0.73
Gender			
Female	0.212	0.15	0.70
Ethnicity			
Caucasian	8.165	95 (20.0)	<0.001
Black	0.511	0.58	0.44
BMI (kg/m^2)			
Pre-donation	0.218	0.40	0.53
First visit	0.025	0.01	0.95
One-year visit	0.054	0.04	0.80
CKD-EPI eGFR (ml/min/1.73m^2)			
Pre-donation	-0.114	3.96	0.04
First visit	-0.270	6.58	0.01
One-year visit	-0.172	4.58	0.03
AER (mg/day)			
Pre-donation	-0.018	0.56	0.45
First visit	0.022	1.95	0.16
One-year visit	-0.063	3.54	0.06
Systolic BP (mmHg)			
Pre-donation	-0.024	0.15	0.70
First visit	-0.021	0.12	0.73
One-year visit	0.550	6.94	0.008
Diastolic BP (mmHg)			
Pre-donation	0.126	1.33	0.25
First visit	-0.111	2.67	0.10
One-year visit	-0.433	4.81	0.03

Abbreviations: BMI, body mass index; CKD-EPI eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; AER, albumin excretion rate; BP, blood pressure; ^{51}Cr-EDTA GFR, Chromium-51-ethylene-diamine-tetra-acetic-acid glomerular filtration rate

Table 2.6 | Accepted donor ethnicity and parameters at most recent follow-up visit

	Caucasian	Black	p-value
Follow-up in years [a]	2.29 (0.56-6.93)	5.54 (1.75-8.84)	0.0028
Parameter at most recent follow-up [b]			
Systolic BP (mmHg)	115.01 (17.53)	121.21 (18.04)	0.008
Diastolic BP (mmHg)	88.75 (13.41)	84.64 (13.07)	0.199
Albuminuria (AER in mg/day)	98.40 (446.22)	47.66 (64.85)	0.298
Serum Creatinine (µmol/L)	104.77 (18.95)	99.07 (21.99)	0.031
CKD-EPI eGFR (ml/min/1.73m^2)	64.44 (15.51)	84.53 (21.33)	<0.0001

Abbreviations: BP, Blood Pressure; AER, albumin excretion rate; CKD-EPI eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation

[a] values are median (± IQR)

[b] values are mean (± SD)

Table 2.7 | Parameters associated with defaulting post-donation follow-up

Parameter	Hazard ratio	95% CI	p-value
Age at donation (in years)			
Age <21	0.2	0.1-0.5	0.001
Gender			
Female	0.7	0.6-1.0	0.1
Male	1.1	0.4-2.9	0.6
Ethnicity			
Black	0.8	0.4-2.0	0.06
Caucasian	2.4	1.2-4.7	0.008
Degree of relationship			
First	2.0	0.7-5.9	0.8
Second	5.9	1.1-31.5	0.1
Third	0.3	0.1-1.5	0.01
Domicile from hospital			
>100 kilometres	1.4	0.8-1.5	0.04

Abbreviations: CI, confidence interval

DISCUSSION

Published data on living donation in Africa is limited, relying on small cohort studies.[34-37] In an analysis of 117 potential donors at a single centre in the Western Cape province of South Africa, the donor exclusion rate was 83%. [34] In the first South African study assessing outcomes of 33 Caucasian related living donors over thirty years ago, [35] a rise in mean diastolic blood pressure with an inclination towards significant decline in creatinine clearance was noted at 5-year follow-up. In a later series by Naicker *et al*.[36], 135 donors with a similar demographic profile to the present study were assessed over a 10-year period. Although limited by 10% of donors being lost to follow-up, no significant difference in blood pressure or proteinuria was noted following donation, with a normal mean serum creatinine level over the follow-up period. Findings of a subsequent study by Abdu *et al*. [37] were similarly reassuring.

This study describes living kidney donation in the context of a developing country. Key findings include:

1. A substantial donor exclusion rate, predominately due to medical contraindications.
2. A significant decline in eGFR amongst a quarter of donors at most recent follow-up (median 3.7 years, IQR 1.2-7.8 years), although none required RRT.
3. Mortality in this series was low and unrelated to the development of renal dysfunction.
4. There was variation in outcomes amongst demographic subgroups, both in the donor evaluation process and in the decline in renal function following donor nephrectomy. Exclusion rates were highest amongst prospective donors of Black African origin. However, no greater risk to Black donors was demonstrated following nephrectomy.

The screening of prospective donors frequently results in the incidental diagnosis of occult disorders. Consistent with previous studies, [17-20] medical contraindications were the most common reason for non-donation in the present cohort, of which undiagnosed hypertension (14%) and obesity (10%) were most prevalent. This reflects the current spectrum of non-communicable disease burden in the local population where hypertension and obesity rates are amongst the highest in sub-Saharan Africa, [38, 39] at 45% and 49% respectively.[40] In addition, epidemiological studies attribute the greatest proportion of disability adjusted life years lost in South Africa to these conditions.[6] The high rates of hypertension and obesity in the failed donor group may partly be due to genetics; numerous studies support the role of distinct heritable factors that contribute to the increased development of these disorders, particularly in populations of black African ancestry. [41-43]

In contrast to developed settings, [17, 20] the present study shows a significant donor exclusion rate due to communicable diseases (6.7%), primarily HIV infection (n=45; 4.9%). The prevalence of HIV amongst potential donors in this cohort is however lower than the general South African population prevalence of HIV infection. In 2016, the estimated adult (aged 15-49 years) seroprevalence rate of HIV in South Africa was 16.6%.[8]

A reduction in donor disqualification rates for medical reasons can be facilitated by improved quality of preventative care provided in primary health care systems.[44] This is of particular relevance with non-communicable diseases, where enhanced screening at a

primary healthcare level may aid the timeous institution of therapy, prior to the development of complications that limit the use of prospective donors. As in our cohort, donors with isolated medical abnormalities including obesity (body mass index 30-35 kg/m^2) and pre-existing hypertension, well controlled on a single agent with no end-organ damage, have been accepted in order to expand living donor pools; recent evidence supports favourable post donation outcomes amongst these subgroups as compared to appropriately matched cohorts. [45, 46]

Immunological barriers resulted in the exclusion of 19% of donor candidates. This represents an important subgroup where novel modalities including paired donor exchanges, potential desensitisation of cross-match positive pairs and ABO-incompatible transplantation may be applied to augment living donation rates.[47, 48] In developed settings, these approaches have increased the utilisation of living donors in otherwise incompatible donor-recipient pairs.[49-51]

Medically suitable donors who voluntarily withdrew accounted for the exclusion of 11.2% of failed donors in this study. Similarly high rates have been reported in multiple centres across the United States.[20, 21] These reports have suggested that enhanced pre-evaluation education programs may reduce the occurrence of donor withdrawal.[52]

Significant variation in the outcome of donor evaluation by ethnicity was demonstrated. Kasembeli *et al.* [53] highlight that black South Africans are at increased risk of chronic kidney disease due to genetic factors, including *APOL1* risk variants. This may account for the disproportionate number of black South Africans on national transplant waiting lists; registry data indicates that 53.2% of patients on RRT in South Africa are of black ethnicity. [8] In the present study, prospective donors from this demographic subgroup were more likely to be excluded from donation, particularly for medical contraindications. As discussed previously, this group also bears an increased risk for hypertension and obesity. Published data on prospective African American donors reflected similar findings. [20,21,54] Weng *et al.* [21] reported that potential donor candidates who are Black are less likely to ultimately donate as compared to Caucasian counterparts; hypertension and obesity predominated as the most common reasons for exclusion.

Moreover, African American donors have been shown to be more likely to decide against donation.[20, 21, 55, 56] As outlined by Purnell *et al.*[57], reasons for this disparity in willingness to donate amongst the African American population include cultural beliefs, perceived medical mistrust and socioeconomic inequality. In this study, donors of Black African descent had the highest voluntary withdrawal rates, likely due to similar reasons. This underscores the need to address unique concerns related to living donation in this subgroup. In developed settings, cost-effective strategies including home visits and the use of social media outlets have proven beneficial in reducing racial disparities in living donor rates. [58, 59] In resource limited settings, these measures can easily be implemented to augment living donor pools amongst this subgroup. In addition, future studies identifying the risks in certain population groups may reduce fears associated with donation.

The presence of new onset hypertension and proteinuria following uninephrectomy are important clinical indicators of potential hyperfiltration injury to remnant glomeruli. As with previous studies, [60, 61] although a statistically significant rise in mean systolic blood pressure was observed following donation, this did not equate overall to clinical hypertension. In our cohort, thirty-eight donors (12.8%) developed new-onset hypertension at most-recent follow-up. The overall prevalence of hypertension in our donor population was however threefold lower than that of the general South African population.[58] Furthermore, albumin excretion rate at last follow-up showed a significant increase but remained within normal limits. One donor (0.3%) developed nephrotic syndrome from causes unrelated to donation.

Although none required the institution of RRT, eighty donors (27%) demonstrated an eGFR less than 60 ml/min/1.73 m^2 at most recent follow-up. This correlated with Caucasian race, the development of hypertension at one-year follow-up and lastly, as in earlier studies, [62, 63] a lower eGFR at baseline. There was also an association with an increased albumin excretion rate at one-year follow-up (p=0.06). Pre-existing hypertension and class I obesity were not shown to be risk factors for developing an eGFR less than 60 ml/min/1.73 m^2 in our cohort. Donors with these isolated medical abnormalities may therefore be utilised more readily in order to expand living donation in our setting. Moreover, the perioperative mortality rate of 0.3% in this study, constituted by one death related to the surgical procedure with the remainder being of causes unrelated to donation, is comparable to that of centres in the United States. [64]

Emerging prospective data from predominantly Caucasian donor cohorts report similar findings.[65-67] Janki *et al*. [65,67] demonstrated excellent donor outcomes at between five and

ten years of donor follow-up. Here, the incidence of hypertension amongst donors was comparable to the general Dutch population and no donors developed proteinuria. In addition, subsequent to the initial expected decline in eGFR immediately following donation, renal function stabilised. As in this cohort, no donor required the institution of RRT and mortality was due to causes unrelated to the development of renal dysfunction.

There is increasing data to suggest a greater risk of CKD in African American donor subgroups.[23-26,68,69] In contrast, over longer post donation follow-up, Black African donors in our cohort demonstrated superior renal outcomes as compared to Caucasian counterparts. This subgroup in fact had better post-donation eGFRs and, although they demonstrated significantly higher systolic blood pressures following donation, mean blood pressure at most recent follow-up was not within the definition of hypertension. This may reflect a conservative approach in the selection of Black African donors in the local setting as their post-donation risks have thus far been poorly defined.

Donor follow-up was poor during the course of the study. This remains a challenge globally as numerous international studies report similarly high lost to follow-up rates.[70-72] Our centre is the only state transplant facility in Johannesburg. Follow-up visits thus necessitate that donors travel considerable distances at personal expense. This may explain the shorter follow-up duration observed among donors who reside further from the hospital. In addition, 16.9% of South Africans are currently members of private medical aid schemes, 72.4% of which are Caucasian.[73] It is therefore possible that Caucasian donors are more readily accessing care within the private healthcare sector. Poor follow-up amongst young donors aged 18-21 years in our cohort may reflect psychological factors, including a lack of

insight regarding the need for follow-up, particularly if they remain asymptomatic. At present, there are no established guidelines outlining the ideal duration and intervals for donor follow-up.[74] Given that close monitoring following donation affords the opportunity for early intervention should concerns arise, measures to ensure life-long follow-up of all kidney donors should be advocated.[75-78]

There are limitations to this study. A relatively short median follow-up duration with a significant lost to follow-up rate may have led to adverse donor outcomes being underestimated. Conversely, adverse outcomes may have been overestimated in the event that symptomatic donors followed up more frequently. Comparative analysis with an appropriately matched control group of non-donors in the South African population would also be of benefit. Follow-up GFR was estimated using the CKD-EPI equation; ideally, if resource constraints were not a limitation, measured GFRs performed using scintigraphy would be preferable as a more accurate assessment of renal function in living donors. In addition, given the demographic profile of potential donors at our centre, genotyping for *APOL1* alleles as a part of the pre-donation risk assessment may potentially be useful if resources allowed. [79, 80]

Strengths of this current study include a comprehensive assessment of living kidney donation in a developing country. As CMJAH is the only state facility that offers transplant services in the greater Johannesburg area, this study provides an accurate overview of living donor assessments and outcomes in this region over more than three decades. Data analysis at various points in donor follow-up allowed for the evaluation of adverse outcomes including the evolution of renal dysfunction following donation. The cohort size allowed

comparison of work-up and post-donation outcomes between different ethnic subgroups. In addition, this study highlights possible ways to expand living donor pools in developing settings. These include population education about donation and addressing reasons for voluntary withdrawal amongst potential donors. An emphasis on the role of early medical care in optimising the treatment of hypertension and the prevention of chronic kidney disease is key, particularly if an increased number of donors with isolated medical abnormalities are to be accepted onto living donor programmes. Furthermore, circumventing immunological barriers to donation with the aid of desensitisation and the introduction of domino transplantation into state facilities is of importance.

In conclusion, this study adds to evidence supporting the ongoing practice of living kidney donation among carefully selected prospective donors. The present study is the largest single-centre report on living kidney donation in sub-Saharan Africa, and is particularly relevant due to the burgeoning demand for a sustainable form of definitive renal replacement therapy in developing countries. In addition, analysis of this cohort does not appear to indicate adverse outcomes for donors of Black African descent.

MATERIALS AND METHODS

This retrospective case cohort study was conducted in the transplant unit of Charlotte Maxeke Johannesburg Academic Hospital, an accredited quaternary level public facility in the Gauteng province of South Africa. The centre is the referral unit for all state hospitals in the greater Johannesburg region. Donor evaluation at the facility is in accordance with existing guidelines. [81, 82]

A record review of all potential living donors assessed since the inception of the centre's living donor program in January 1983 to July 2015 was conducted. In the present analysis, information gathered for all potential living donors included demographics, relation to the intended recipient and the outcome of the eligibility evaluation. If excluded from living donation, the reason for non-donation was documented. For accepted living donors, clinical and laboratory parameters including body mass index, blood pressure, albumin excretion rate and serum creatinine were recorded at baseline and at various points in donor follow-up. Any pre-existing medical condition(s) were noted. Hypertension following donation was defined as per documentation of either the diagnosis in medical records or the use of anti-hypertensive therapy. The albumin excretion rate was assessed by 24-hour urine collection or a spot urine albumin-creatinine ratio. All laboratory investigations were performed at a single facility. Measured pre-donation GFRs, as defined by chromium-51-ethylene-diamine-tetra-aceticacid scans, were noted. Pre- and post-donation eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[83] Domicile in relation to the transplant centre, the number of post-donation follow-up visits and the last follow-up date were recorded. If last follow-up was more than six months before the study end-point (31-07-2015), donor defaulting was assumed. The reason for lost to follow-up was recorded where known. Mortality data was collected for accepted living donors that demised during the study period.

Statistical analyses were performed using Statistica for Windows version 12.0 (Statsoft Inc., 2015, Tulsa, OK, USA). Distribution was assessed by the Shapiro Wilk W test and visual inspection of the normogram. Continuous variables are expressed as means and standard deviations or medians and interquartile ranges, where distributions were Gaussian or non-

Gaussian respectively. Categorical variables are presented as percentages. Statistical comparisons were performed with the Student's t-test for continuous normally distributed variables and the chi-squared test for categorical variables. Where appropriate, the one-way ANOVA and Wilcoxon matched pairs testing were applied. For the accepted donor cohort, a multiple linear regression analysis was performed to identify independent factors associated with a reduced eGFR of <60 ml/min/1.73 m^2 at last follow-up. The Cox proportional hazard model was applied to assess variables which impacted on donor follow-up. A p-value of less than 0.05 was considered to indicate statistical significance. This study was approved by the Committee for Human Research of the University of the Witwatersrand (Clearance Certificate Number: M150923).

DISCLOSURE

All the authors declared no competing interests.

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CHAPTER 3: APPENDICES

APPENDIX A

Data Collection Sheets

i. Data collection sheet for failed living donors

STUDY NUMBER		
RELATION TO INTENDED RECIPIENT	☐ RELATED	☐ PARENT ☐ SIBLING ☐ CHILD ☐ OTHER RELATIVE
	☐ UNRELATED	☐ SPOUSE ☐ FRIEND ☐ OTHER
	☐ ALTRUISTIC	
DEMOGRAPHIC DATA OF POTENTIAL DONOR	**GENDER**	☐ MALE ☐ FEMALE
	ETHNICITY	☐ CAUCASIAN ☐ BLACK ☐ ASIAN ☐ OTHER / MULTI-RACIAL
	AGE AT ASSESSMENT	☐ 18 – 21 ☐ 22 – 29 ☐ 30 – 39 ☐ 40 – 49 ☐ 40 – 49 ☐ ≥ 60
FAMILY HISTORY		
OUTCOME OF POTENTIAL DONOR EVALUATION	☐ ACCEPTED FOR LIVING DONATION- ultimately did not donate	** SPECIFY REASON(S) FOR EXCLUSION IN SECTIONS WHICH FOLLOW*
	☐ REJECTED FOR LIVING DONATION	
RENAL BIOPSY PERFORMED ON POTENTIAL LIVING DONOR	☐ YES	INDICATION: _____ RESULT:_____
	☐ NO	

REASONS FOR DONOR EXCLUSION

DONOR-RECIPIENT RELATED

☐ ABO INCOMPATIBILITY ☐ CYTOTOXIC ANTIBODY CROSS-MATCH

DONOR RELATED

MEDICAL		UROLOGICAL	RADIOLOGICAL	PSYCHOSOCIAL
METABOLIC PROFILE	☐ OBESITY (BMI >35) ☐ HYPERTENSION ☐ DIABETES	☐ HAEMATURIA ☐ RECURRENT UTIs ☐ NEPHROLITHIASIS ☐ HYDRONEPHROSIS ☐ ELEVATED PSA ☐ OTHER Specify:	☐ RENAL CYSTS ☐ ABNORMAL RENAL VESSELS ON CTA ☐ OTHER ANATOMICAL DEFECTS Specify:	☐ REQUIRED REFERRAL TO : - SOCIAL WORKER - PSYCHOLOGIST - PSYCHIATRIST ☐ WITHDREW VOLUNTARILY ☐ LOST TO FOLLOW-UP Specify Reason:
RENAL	☐ ↓ GFR or CrCL ☐ PROTEINURIA			
VIROLOGY AND INFECTION SCREEN	☐ HIV ☐ TB ☐ EBV ☐ CMV ☐ HepBsAg (+) ☐ HepCAb (+)			
HIGH CARDIOVASCULAR RISK	☐ IHD ☐ PREVIOUS ACS ☐ VALVULAR HEART DISEASE ☐ HEART FAILURE ☐ ARRYTHMIA			
RESPIRATORY DISEASE	☐ ASTHMA ☐ COPD			
INCIDENTAL MALIGNANCY	Specify:			

RECIPIENT RELATED

TRANSPLANT CANDIDATE	☐ MEDICALLY INELIGIBLE ☐ DEMISED
ALTERNATIVE DONATION RECEIVED	☐ FROM DECEASED DONOR ☐ ALTERNATE LIVING DONOR

MISCELLANEOUS (Specify any other reasons for donor exclusion)

ii. Data collection sheet for accepted living donors

STUDY NUMBER		
RELATION TO RECIPIENT	☐ RLD – Specify _____ ☐ NRLD (Directed) – Specify _____ ☐ NRLD (Non-directed)	
DEMOGRAPHIC DATA OF ACCEPTED DONOR	**GENDER**	☐ MALE ☐ FEMALE
	ETHNICITY	☐ CAUCASIAN ☐ BLACK ☐ INDIAN ☐ OTHER
	AGE AT DONATION	
FAMILY HISTORY		
DATE OF DONATION		
LAST FOLLOW-UP DATE		
NUMBER OF POST-DONATION FOLLOW-UP VISITS		
DOMICILE	☐ <100km ☐ >100km	
LOST TO FOLLOW-UP	☐ YES ☐ NO	
REASON FOR LOST TO FOLLOW-UP (if known)		

PRE-DONATION DATA

BASELINE CHARACTERISTICS AT DONATION		
BMI (kg/m²)	☐ < 25 ☐ 25 – 29 ☐ 30 – 35	
ALBUMIN EXCRETION RATE (mg/day)	☐ A1: < 30 ☐ A2: 30 – 300	
SBP (mmHg)	☐ < 120 ☐ 120 – 139 ☐ ≥ 140	
DBP (mmHg)	☐ < 80 ☐ 80 – 89 ☐ ≥ 90	
PRE-EXISTING CONDITION(S)		
BASELINE SERUM CREATININE (µmol/L)	Specify value: _____	
eGFR (in ml/min/1,73m²)	**^{51}Cr EDTA Scan**	☐ 70 – 79 ☐ 80 – 89 ☐ ≥ 90
	CKD-EPI Formula	☐ 70 – 79 ☐ 80 – 89 ☐ ≥ 90
HABITS	**SMOKING STATUS**	☐ Smoker ☐ Non-smoker Number of Pack Years: _____
	ALCOHOL CONSUMPTION	☐ YES ☐ NO

POST-DONATION DATA

CHARACTERISTICS AT FOLLOW-UP			
AGE AT FOLLOW-UP		**FOLLOW-UP VISIT**	☐ FIRST VISIT POST-DONATION ☐ 1 YEAR ☐ MOST RECENT VISIT
ALBUMIN EXCRETION RATE (mg/day)	☐ A1: < 30	☐ A2: 30 – 300	☐ A3: > 300
SBP (mmHg)	☐ < 120	☐ 120 – 139	☐ ≥ 140
DBP (mmHg)	☐ < 80	☐ 80 – 89	☐ ≥ 90
SERUM CREATININE (µmol/L)	Specify value: _____		
eGFR by CKD-EPI Formula (in ml/min/1,73m²)	☐ G1: ≥ 90 ☐ G3a: 45 – 59 ☐ G4: 15 – 29	☐ G2: 60 – 89 ☐ G3b: 30 – 44 ☐ G5: < 15 (please complete below)	
	FOR eGFR <15	Years from donation to ESRD	_____ years
		Specify RRT	☐ On waiting list for dialysis ☐ On dialysis ☐ Received transplant
HABITS	**SMOKING STATUS**		☐ Smoker → Pack Years _____ ☐ Non-smoker
	ALCOHOL CONSUMPTION		☐ YES ☐ NO
DEVELOPMENT OF CO-MORBID DISEASE	☐ NEW ONSET HYPERTENSION ☐ NEW ONSET DIABETES ☐ OTHER _____		
HISTORY OF NEPHROTOXIC DRUG INTAKE	☐ NSAIDs	☐ OTHER _____	

MORTALITY DATA

AGE AT DEATH	
TIME FROM DONATION TO MORTALITY	_____ years
CAUSE OF DEATH	☐ RENAL DISEASE ☐ CARDIOVASCULAR EVENT ☐ OTHER _____

APPENDIX B

Ethics clearance certificate

R14/49 Dr Chandni Dayal

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150923

NAME: (Principal Investigator)	Dr Chandni Dayal
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Evaluation of Potential Kidney Donors and Outcomes Post-Donation at Charlotte Maxeke Johannesburg Academic Hospital (1983 - 2015)
DATE CONSIDERED:	02/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Nina Diana and Dr Malcolm Davies

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/10/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

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 resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 10/10/15

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C

Plagiarism report

The plagiarism software Turn-it-in was used to review this dissertation. A similarity index of 12% was reported. This relates to the use of standard definitions. Furthermore, all other similarities have been appropriately referenced.

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HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
Division of Nephrology
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Postgraduate Studies Committee
Faculty of Health Sciences
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To whom it may concern

Re: Turn-it-in report for Dr. Chandni Dayal MMed: 'Evaluation of potential kidney donors and outcomes post donation at Charlotte Maxeke Johannesburg Academic Hospital (1983 – 2015)'

I have reviewed the Turn-it-in report of Dr. C Dayal's MMed dissertation. The report identifies a similarity index of 12%. Much of this is related to the use of standardized definitions and terms. All information that bears a similarity has been appropriately referenced.

Regards

Diana

Dr. N Diana
Consultant Nephrologist
CMJAH
(Dr. Dayal's MMed supervisor)