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The impact of deceased versus living donor graft status on kidney transplant outcomes: A Johannesburg single-center 48 years experience of 1,685 patients

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Abstract

Background: This study is aimed to determine the impact of living donor (LD) versus deceased donor (DD) kidney transplantation on renal graft survival and patient overall survival rates within Johannesburg, South Africa.

Materials and methods: A retrospective assessment was conducted of all 1,685 adult first kidney-alone kidney transplant recipients transplanted between the years 1966 and 2013 in a single center. The patients were divided according to the source of the transplant: LD versus DD. Demographics and post-transplantation follow-up data were determined and tabulated. Graft and overall survival plots were generated.

Results: Of the recipients enrolled, 84.1% were DD recipients and 15.9% were LD recipients. LD recipient status was significantly associated with younger age ($p \leq 0.0001$), a higher proportion of white, Asian, or mixed race compared to black race ($p \leq 000.1$), a higher proportion of urologic etiology of disease ($p = 0.015$), and a lower proportion with hypertension ($p \leq 0.0001$) as the cause of ESKD. Results showed a decreased risk of graft failure (HR 0.55; 95% CI 0.45–0.66) and a decreased risk of death (HR 0.47; 95% CI 0.36–0.61) among LD graft recipients as compared to DD graft recipients.

Conclusions: In keeping with internationally reported trends, LD recipients continue to have enhanced patient and graft survival outcomes as compared to DD recipients within our local experience. This Johannesburg experience will serve as a foundation for future related studies in this region of the world.

Keywords: Graft survival; Kidney transplant; Living donors; South Africa; Survival rate

1. Introduction

Worldwide, solid organ failure is a significant public health problem. Without access to treatment, the outcomes of those affected are uniformly fatal. Compared to high-income countries, many with organ failure in low and middle-income countries do not have access to treatment, leading to higher rates of premature death and increases in Disability-Adjusted Life Years.[1] Furthermore, establishing and sustaining care for organ failure in resource-limited settings is challenging. These challenges pertain to shortages of organ donors, limited capacity in terms of human resource-intensive services and health systems infrastructure, restricted health care budgets, and pervasive sociodemographic inequalities that disproportionately affect the poor. For example, those with health insurance or living in urban areas are more likely to access care than their rural or uninsured counterparts.

In the case of kidney failure, also known as end stage kidney disease (ESKD), treatment includes chronic dialysis therapy and kidney transplantation, with both modalities comprising kidney replacement therapy (KRT). Kidney failure portends significant mortality, morbidity, and reduced quality of life. Kidney transplantation is the best treatment option to enhance survival, improve quality of life, and is more cost-effective than chronic dialysis therapy. In 2010, global estimates calculated that at least 4 million people required KRT but only half received it—with the largest treatment gaps in low income countries, particularly in Asia and Africa.[1]

In sub-Saharan Africa few countries provide access to KRT, mostly in the form of chronic dialysis, and even fewer have transplant programs. Based on the prevalence of diabetes and hypertension, only 1.5% of those in sub-Saharan Africa requiring KRT receive appropriate care, and of these, mortality is high owing to late presentation, discontinuation of dialysis due to lack of funding, as well as poor dialysis quality.[2] Within a South African context, systemic inequalities in a two-tiered health care system, low deceased organ donation rates, and lack of government commitment to support transplantation has led to regression in the provision of KRT.[3] While access to chronic dialysis therapy has improved to 186 per million population, mostly through the

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private sector, during the same year, only 236 kidney transplant procedures were performed nationally. The majority of these transplants were performed in Gauteng and the Western Cape, with just over half from deceased donors.[4]

Globally, and in South Africa, poor rates of deceased donation (DD) require urgent attention, however, an alternative is to increase living donor (LD) kidney transplantation, which has been associated with better outcomes. In the United States, for example, in 2017, the one year survival rate for LD grafts was 96.9% compared to a 93.0% one year survival rate for DD grafts.[5] Despite numerous challenges, kidney transplantation has a long history in South Africa, beginning in Johannesburg in 1966. The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is part of the University of Witwatersrand's academic Teaching Hospital complex and is one of the core kidney transplant centres in the country. There is scant recent published data from CMJAH comparing outcomes for recipients with DD versus LD grafts.[6] In this study, we describe the experience of living and deceased donor kidney donation at CMJAH since inception of the kidney transplant program.

2. Materials and methods

We performed a retrospective review of all adult first kidney-alone transplant recipients who received a LD or DD donor graft between 1966 and 2013 at CMJAH. The study was approved by the Medical Human Research Ethics Committee, University of Witwatersrand (M121186) and records were accessed electronically, using REDCap.[7,8] Because of changes in maintenance immunosuppression regimens used in the transplant unit over time, we divided the cohort into three eras. Era 1 (1966–1983) involved dual therapy with corticosteroids and azathioprine; Era 2 (1984–2000) involved a triple therapy regimen of corticosteroids, azathioprine, and cyclosporine; and Era 3 (2001–2013) was characterized by the introduction of alternatives to azathioprine, such as mycophenolic acid, second-generation calcineurin inhibitors, such as tacrolimus, and, with certain indications, mammalian target of rapamycin (m-tor) inhibitors.

2.1. Data collection

For this analysis, we used the following variables: Donors: age, sex, blood group (ABO), and graft donor status (living or deceased). Recipients (at the time of transplant): date of transplant procedure, age at transplant, sex, blood group (ABO), self-reported ethnicity, diabetes status at transplant, and etiology of ESKD. ESKD was classified as: biopsy-proven primary glomerular disease, biopsy-proven secondary glomerular disease, urologic causes, hereditary causes, anatomic causes. For recipients surviving at least 1 year after transplant: number of biopsy-proven acute rejection episodes (in the first year), number and type of surgical complications (in the first year); presence or absence of hypertension at 1, 3, and 5 years; hypertension was defined as a systolic blood pressure $\geq$140 mm Hg. For recipients with functioning grafts: graft function was assessed using the CKD-EPI equation[9] without the African American co-efficient to calculate a creatinine-based estimated glomerular filtration rate (GFR) at 6 months and 1, 3, and 5 years post-transplant. For survival analyses, data collected included date of death, date of graft loss, or most recent visit date.

2.2. Statistical analysis

Descriptive statistical analysis was conducted using proportions to represent categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) to represent numerical variables, as appropriate. Comparison of categorical variables by donor type, controlling for transplant era, was conducted using the Cochran-Mantel-Haenszel test. Comparison of continuous study variables by donor type, controlling for transplant era, was conducted using a General Linear Model with donor type and transplant era as independent variables. The effect of donor type on recipient and graft survival, unadjusted and adjusted for recipient age at transplant, gender, ethnicity, pretransplant diabetes, and transplant era, was assessed by Cox proportional hazards regression. For recipients alive at 5 years post-transplant, comparison of eGFR between post-transplant time points, donor type, and their interaction was achieved by using a repeated-measures mixed model with eGFR as the dependent variable, donor type and time as fixed effects and recipient as a repeated measure. Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

3. Results

During the study period, 1,685 adult first kidney-only transplant procedures were performed; most recipients were white males. By far, the majority of grafts were from DD. Overall, donors were relatively young (<30 years old); the mean age of DD was significantly younger than LD. While more DD were male, the majority of LD were female. For black recipients, a smaller proportion received LD grafts as compared to other ethnic groups. When comparing transplant eras, the largest overall number of transplant procedures were performed during Era 2; relatively more LD transplants were performed during Era 3. Table 1 summarizes characteristics of recipients and donors, overall and according to donor status (deceased and living).

3.1. Graft survival

Overall, across the three eras, median survival for all grafts was 5.2 years (IQR 4.5–5.9). However, median graft survival for DD grafts (4.3 years; IQR 3.5–4.9) was substantially lower than for LD grafts (11.3 years; IQR 8.8–13.5). Using the Kaplan–Meier method, we compared DD and LD graft survival at 1, 5, and 10 years post-transplant (Fig. 1). Unadjusted, there was a decreased risk of graft loss for LD graft recipients (HR 0.55; 95% CI 0.45–0.66) and this remained significant after adjusting for age at transplant, sex, self-reported ethnicity, diabetes at the time of transplant, and transplant era (HR 0.61; 95% CI 0.50–0.74) (Table 2).

3.2. Recipient survival

For adult recipients, there was a decreased risk of death for recipients of LD kidney grafts (HR 0.47; 95% CI 0.36–0.61), and this remained significant after adjusting for age at transplant, gender, ethnicity, diabetes and transplant era (HR 0.61; 95% CI 0.47–0.79) (Table 3). Using the Kaplan–Meier method, we compared DD and LD recipient survival at 1, 5, and 10 years post-transplant (Fig. 2). We observed a higher risk for graft loss and death in recipients who had diabetes mellitus at the time of transplant, and in those who were older, female, and self-reported black or Asian ethnicity (as compared to white recipients). In addition, we observed a decreased risk of death in Eras 2 and 3, as compared to Era 1 (Tables 2 and 3). For recipients surviving to at least 1 year, those who received LD grafts had significantly lower rates of hypertension than those who received DD grafts at 1 year ($p < 0.001$) and 3 years ($p < 0.001$), but this difference was attenuated at 5 years post-transplant ($p = 0.76$).

Table 1

Clinical characteristics of kidney-alone first transplant recipients, overall and by deceased or living donor status.

	Overall	DD graft	LD graft	*p*-value: between group test
Variable	n	n (%)	n (%)	
Sample size (missing n = 4)	1,685	1,413 (84.1)	268 (15.9)	
Transplant era				0.020
Era 1 (1966–1983)	458 (27.2)	388 (27.5)	69 (25.7)	
Era 2 (1984–2000)	914 (54.2)	779 (55.1)	133 (49.6)	
Era 3 (2001–2013)	313 (18.6)	246 (17.4)	66 (24.6)	
[a]Recipient age (years)	38 (10)	39 (11)	33 (9)	<0.0001
Recipient sex				<0.12
Female	651 (38.6)	535 (37.9)	114 (42.5)	
Male	1,034 (61.4)	878 (62.1)	154 (57.5)	
Recipient ethnicity (self-reported) (missing n = 6)				<0.0001
White	951 (56.6)	781 (55.5)	168 (62.9)	
Black	516 (30.7)	457 (32.5)	57 (21.3)	
Mixed race	117 (7.0)	93 (6.6)	24 (9.0)	
Asian	95 (5.7)	77 (5.5)	18 (6.7)	
Etiology of ESKD (missing n = 184; etiologies sum to >1,685 as there may have been more than one etiology per recipient)				
Kidney disease	780 (52.0)	650 (51.3)	129 (54.4)	<0.10
Hypertension	489 (32.6)	429 (33.8)	59 (24.9)	<0.0001
Urologic	127 (8.5)	98 (7.7)	29 (12.2)	0.015
Inherited	126 (8.4)	102 (8.0)	24 (10.1)	0.19
Anatomic	14 (0.9)	11 (0.9)	3 (1.3)	0.51
Other	29 (1.9)			
Diabetes at time of transplant (missing n = 50)				0.16
Yes	107 (6.5)	85 (6.2)	22 (8.5)	
No	1,528 (93.5)	1,286 (93.8)	238 (91.5)	
[a]Donor age (years)	29 (14)	28 (14)	35 (9)	<0.0001
Donor sex (missing n = 123)				<0.0001
Female	508 (32.5)	374 (28.6)	134 (53.4)	
Male	1054 (67.5)	935 (71.4)	117 (46.6)	
ABO compatibility (missing n = 75)				0.021
Compatible	1,397 (86.8)	1,197 (87.6)	198 (81.8)	
Incompatible	213 (13.3)	169 (12.4)	44 (18.1)	
Biopsy-proven acute rejection episodes in first year post-transplant				0.19
0 episodes	1,328 (78.8)	1,106 (78.3)	218 (81.3)	
1 episode	303 (18.0)	258 (18.3)	45 (16.8)	
≥ 2 episodes	54 (3.2)	49 (3.5)	5 (1.9)	
[b]Surgical complications in first year post-transplant				
[c]Wound-related	325 (20.8)	264 (20)	52 (3.9)	0.78
Native nephrectomy at transplant	150 (9.6)	129 (9.8)	21 (1.6)	0.66
[d]Ureteric	155 (9.9)	128 (9.8)	26 (2)	0.85
Infarcted/clotted graft	44 (2.8)	36 (2.7)	8 (0.6)	0.53
Other	71 (4.5)			

[a] Age (years): denoted as mean (standard deviation).
[b] Surgical complications: the following frequencies of complications were too small for inclusion in the analysis: renal artery thrombosis (n = 21); renal vein thrombosis (n = 19); incisional hernia (n = 14); lymphocele (n = 13); renal artery stenosis (n = 4); renal vein stenosis (n = 3).
[c] Wound-related complications included: wound sepsis (including abscess), wound hematoma or hemorrhage, and wound dehiscence.
[d] Ureteric complications included: sloughed ureter, urine leak, urinoma, and ureteric obstruction.

3.3. Graft function post-transplant

We assessed graft function longitudinally after transplant using serial measurements of serum creatinine to estimate GFR. We found no significant association between donor type, time post-transplant, or their interaction with post-transplant graft function ($p = 0.44$, 0.52, and 0.66, respectively). Removal of the interaction term showed that neither donor type nor time significantly affected mean eGFR ($p = 0.36$ and 0.58, respectively). The mean eGFR, together with its 95% CI (denoted by error bars) is plotted as a function of time, stratified by donor type. The mean change in eGFR between each time point, together with its 95% CI (denoted by error bars) is plotted as a function of time, stratified by donor type.

4. Discussion

Our study of adult first kidney-alone transplants from a large transplant center in Johannesburg, South Africa, shows that recipient and graft survival has improved with time, and recipient and graft survival rates after LD transplant are better than after DD transplant. Our findings align with the global kidney transplant community, where consistent improvements in recipient and graft outcomes have occurred, largely attributed to improvements in immunosuppressive protocols as well as patient care.[10] Nonetheless, donor source remains an important factor influencing short- and long-term graft outcomes as well as patient survival[6,11,12] and assumes particular importance in the South African context, given the consistently low

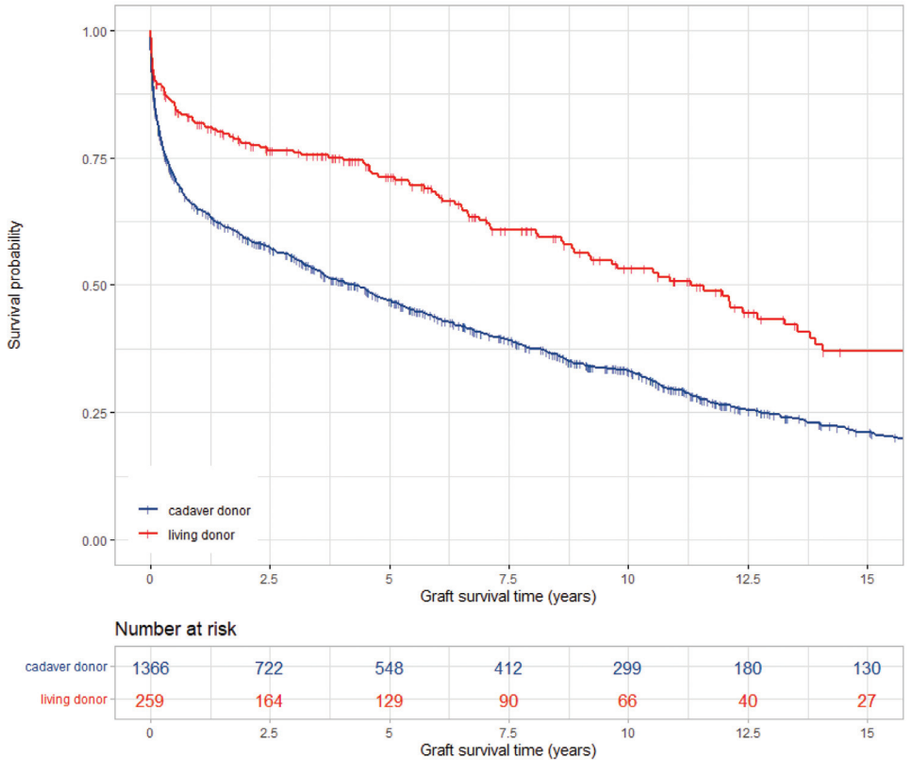

Figure 1. Kaplan–Meier plot comparing living and deceased donor graft survival (n = 1,625). One, 5, and 10 years DD graft survival was 64.9% (95% CI 62.3–67.4%); 47.0% (95% CI 44.2–49.7%); and 33.2% (95% CI 30.5–35.9%), respectively. One, 5, and 10 years LD graft survival was 81.8% (95% CI 76.4–86.0%); 71.3% (95% CI 64.9–76.7%); and 53.3% (95% CI 45.6–60.4%), respectively.

Table 2

Factors impacting kidney graft survival.

	p	Hazard ratio for graft failure	95% CI for HR
Unadjusted			
Donor type			
Cadaver		1	Reference
Living	<0.0001	0.55	0.45–0.66
Adjusted			
Donor type			
Cadaver		1	Reference
Living	<0.0001	0.61	0.50–0.74
Transplant era			
1966–1983 (Era 1)		1	Reference
1984–2000 (Era 2)	0.020	0.84	0.73–0.97
2001–2013 (Era 3)	<0.0001	0.43	0.34–0.56
Recipient age at transplant (per year)	<0.0001	1.01	1.01–1.02
Recipient sex			
Male		1	Reference
Female	0.87	1.01	0.89–1.14
Recipient self-reported ethnicity			
White		1	Reference
Black	<0.0001	1.41	1.20–1.66
Mixed	0.22	1.16	0.92–1.47
Asian	0.0042	1.41	1.20–1.66
Diabetes at time of transplant			
No/unknown		1	Reference
Yes	0.045	1.26	1.01–1.58

Table 3

Factors impacting recipient survival.

	p	Hazard ratio for death	95% CI for HR
Unadjusted			
Donor type			
Cadaver		1	Reference
Living	<0.0001	0.47	0.36–0.61
Adjusted			
Donor type			
Cadaver		1	Reference
Living	0.0003	0.61	0.47–0.79
Transplant era			
1966–1983 (Era 1)		1	Reference
1984–2000 (Era 2)	<0.0001	0.68	0.57–0.82
2001–2013 (Era 3)	<0.0001	0.32	0.23–0.45
Recipient age at transplant (per year)	<0.0001	1.04	1.04–1.05
Recipient sex			
Male		1	Reference
Female	0.022	1.20	1.03–1.40
Recipient self reported ethnicity			
White		1	Reference
Black	<0.0001	1.67	1.36–2.06
Mixed	0.81	0.96	0.69–1.34
Asian	0.0011	1.75	1.25–2.44
Diabetes at time of transplant			
No/unknown		1	Reference
Yes	0.0001	1.69	1.29–2.20

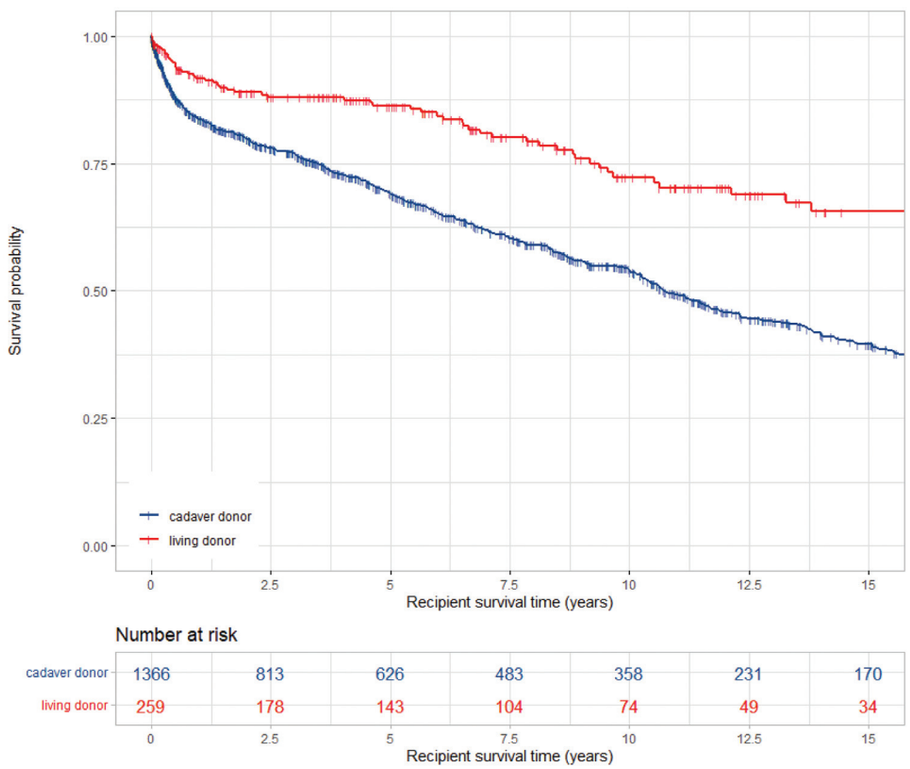

Figure 2. Kaplan–Meier plot comparing living and deceased donor recipient survival (n = 1,625). One, 5, and 10 years DD recipient survival was 83.6% (95% CI 81.5–85.6%); 69.1% (95% CI 66.2–71.7%); and 54.0% (95% CI 50.7–57.2%), respectively. One, 5, and 10 years LD recipient survival was 91.7% (95% CI 87.4–94.6%); 86.3% (95% CI 81.0–90.2%); and 72.3% (95% CI 64.4–78.7%), respectively.

rates of deceased organ donation that hinder national transplant rates.

Enhanced survival for LD versus DD kidney transplants is well described and attributed to multiple factors, including reduced waiting time on transplant lists, the elective nature of the LD procedure with donor and recipient health status optimized presurgery,[13] minimal cold ischemic time,[11,13] the absence of brain death in the donor, and an increase in transplanted nephron mass.[13] While addressing these factors was not in the scope of this study, we demonstrated lower rates of hypertension after transplant for those who received LD grafts. One potential explanation is the development of transplant renal artery stenosis which presents as refractory hypertension (75.8%) and allograft dysfunction (37.9%). It is interesting to note that transplant renal artery stenosis has been more frequently reported in DD recipients, whose cold ischemic time is longer.[14]

The presence of comorbid systemic conditions is associated with poor long-term patient survival after kidney transplantation. In contrast, recipients with primary glomerular causes of ESKD fare better post-transplant. Our study corroborates these findings by demonstrating relatively poor graft survival in those with pretransplant diabetes. Other studies have demonstrated that for patients with type 2 diabetes, the 5-year survival rate was lower than for those without diabetes (70% vs. 93%). It was shown that this difference could be attributed to an older age at time of transplant, a higher body mass index, and a higher incidence of cardiovascular events post-transplant.[15]

Early data collected on kidney transplantation demonstrated decreased graft and patient survival rates among African-American recipients.[13] Those findings are reinforced by our study, in which there was a higher risk of both graft failure and mortality among Black and Asian recipients as compared with White recipients. While the reasons for these findings are not completely understood, various hypotheses for adverse outcomes in African-Americans have been debated in the literature, some of which include an increased risk of rejection due to increased rates of human leukocyte antigen mismatches, fewer LD grafts, pharmacogenomic variants that result in different rates of metabolism of immunosuppressive agents such a calcineurin-inhibitors, socioeconomic disparities, inadequate medical insurance for post-transplant care, and certain genetic factors, such apolipoprotein L1 risk variants that increase the risk of graft failure.[13] While none of these factors have been specifically evaluated in our study, they should be considered as a focus for future research.

There are limitations to this study. As kidney transplant recipients are impacted by multiple simultaneous variables and extraneous factors, it is difficult to interpret which dependent variable has the most significant effect on graft and patient survival. Although post-transplant data on the prevalence of hypertension was available, it is unclear how many of these patients had pre-existing hypertension prior to transplant. Furthermore, our study is from a single transplant centre in South Africa, and therefore may not be representative of the national experience. In addition, the majority of transplant recipients in the study sample were white (56.6%), which is not representative of the population distribution in South Africa.

Our study may inform directions for future research on kidney transplantation in South Africa, perhaps most noteworthy of which would be an in-depth exploration of observed differences in outcomes among ethnic groups, which could include factors such as human leukocyte antigen mismatch, apolipoprotein L1 genotype, phenotypic risk, socioeconomic and demographic characteristics, and pharmacogenomic responses to immunosuppressive therapy.

5. Conclusion

In a large transplant center in Johannesburg, South Africa, survival for adult kidney transplant recipients and their grafts has improved substantially with time. LD grafts, as compared to those from DD, are associated with better recipient and graft survival. These findings underscore the need for enhancing efforts to promote living donation, especially given the persistent shortage of DD organs in this country.

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Statement of ethics

The study was approved by the Medical Human Research Ethics Committee, University of Witwatersrand (M121186). The study was a retrospective record review over a 48 year period. According to the University of the Witwatersrand, participant consent was not required in this study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

The authors have no conflict of interest.

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Author contributions

June Fabian: Study concept and design, acquisition of data, critical revision of the manuscript, administrative, technical and material support, study supervision; Ahmed Adam: Study concept and design, drafting the manuscript, critical revision of the manuscript, administrative, technical and material support, study supervision; Tanya Milwid: Drafting the Manuscript, critical revision of the manuscript.

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