Patient And Allograft Survival After Transplantation With A Living Donor Kidney: 14 Years Experience*.

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BACKGROUND: **Late allograft loss remains a key area of concern. This study was aimed at determining the patient and renal allograft outcome and identifying the factors responsible for survival following transplantation with a living-related donor kidney at the Nairobi Hospital, Kenya.**
METHODS: **Follow-up data for living-related donor graft recipients between 1988 and 2001 was collected. Outcome measures studied were patient and graft survival. Graft loss was defined by the need for permanent renal dialysis, repeat transplantation or death with a functioning graft. The Kaplan-Meier method was used to estimate survival. Crude mortality rates per 100 person-years of follow-up were also calculated. Outcome status was correlated with age, sex, readmission, creatinine level, duration of follow-up and financial sustainability. The Fischer's exact test, X^2 analysis and t-test were employed where appropriate. Logistic regression was used to detect independent risk factors for outcome. $P < 0.05$ was considered significant.**
RESULTS: **Follow-up data were available for 45 of 53 patients. Six were subsequently lost to follow-up. The 1-year and 5-year patient survival was 77.8 and 63.1 % respectively. The overall mortality was 10.7 per 100 person-years of follow-up. Risk of mortality was higher in the first year after transplantation (approximately double). Female gender, elevated serum creatinine levels, readmission and non-sustainable finances adversely affected patient outcome on univariate analysis. Overall graft survival was 77.8 % at 1 year and 52.7 % at 5 years. Most Deaths resulted from chronic allograft rejection and sepsis.**
CONCLUSION: **Pharmacological manipulations with newer immunosuppressive agents could reduce allograft loss and impact positively on patient survival.**

Introduction

The Important outcome measures to consider in renal transplantation analyses are patient and graft survival. There has been considerable improvement in patient survival over the last three decades with current global estimates of 95 percent and 90 percent survival at 1 and 5 years respectively[1]. The main determinants of this survival are however still not completely understood. Some results suggest older age of recipients, the male gender, the presence of diabetes and hypertension and cigarette smoking as the negative determinants of patient survival[1,2]. With regard to graft outcome, both the short and long-term allograft survival has improved. This outcome has depended mainly on the quality of immunosuppression. The short-term outcome has been more substantial and attributable to the introduction of cyclosporin and OKT3 monoclonal antibody in the 1980s[3,4] and more recently, mycophenolate mofetil and tacrolimus[5,6]. The relative risk of mortality for living donor transplant recipients is much less compared to cadaver transplant

recipients[2]. The one- year survival rates now range between 80 and 90 percent[4,7].

Late allograft loss continues to be of concern. Chronic allograft nephropathy and death with a functioning graft are key underlying factors in this late loss. Our study sought to determine the long-term patient and renal-allograft survival and to identify factors that may affect survival at the Nairobi hospital.

Patients and methods

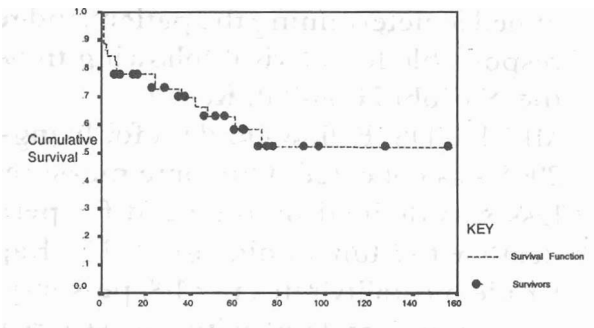
We studied all adults who underwent live donor renal transplantation between 1988 and 2001 at the Nairobi hospital. Details on donor and recipient characteristics as well as the transplant protocol at the hospital were brought out in earlier publications[8,9]. A hospital transplant database does not exist. The authors therefore obtained follow-up data from individual physicians looking after the recipients post-operatively. Graft loss was defined by need for permanent dialysis, repeated transplantation or death with functioning graft. The Kaplan-Meier Method was used to estimate the survival of the patients and their grafts during follow-up. Short-term survival for both graft and patient was defined as survival for a period less or equal to one year. Long-term survival was that for longer than one year.

Variables in the analysis included socio-demographic, clinical and transplant-related data. The crude mortality rates per 100 person years of follow-up were calculated. Outcome status was correlated with age, sex, readmission, co-morbidity, and serum level of creatinine, rejection episodes, financial sustainability, and compliance with medication, follow-up duration and the cause of end-stage renal failure. The Fischer's exact test and X^2 analysis were used to determine statistical significance. Calculation of differences in lengths of follow-up, and average creatinine levels and age was determined by the t-test. Stepwise binary logistic regression was used to detect independent risk factors for poor outcome. Statistical significance of differences in survival distribution was determined by log-rank analysis. The data was presented in the form of frequency tables, charts and survival plots.

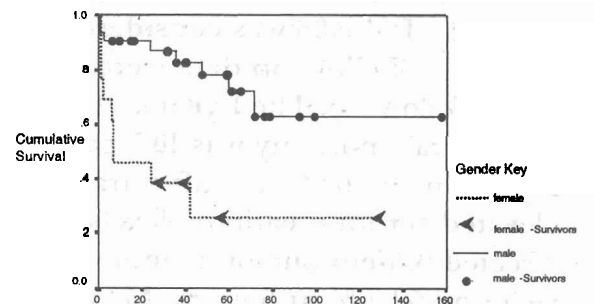
Results

Follow-up data were available for 45 (44 first time and one re-transplantations) out of 53 eligible allograft recipients. The recipients (average age 42.0±11.81 years) were followed up for a total of 1900 months (mean follow-up duration 42.22 months; range 1-158 months). Six patients (13%) did not complete the follow-up. The 1-year and 5-year patient survival for this cohort was 77.8 and 63.1 percent respectively. The calculated overall mortality rate was 10.7 per 100 person years of follow-up. There were more deaths in the first year after transplantation than during follow-up beyond one year. The mortality rate was 22.2/100 person-years of follow-up within the first post-transplantation year and 5.79/100 person-years thereafter. This difference in survival between the first and subsequent years of follow-up was statistically significant (p = 0.003, odds ratio 3.16, C/I 1.52-6.57) on univariate analysis.

Fig.1 Patient Survival Plots After Renal Transplantation At Nairobi Hospital.



Overall Kaplan-Meir survival curve.



Kaplan-Meir plot of survival of males and females

Table 1: Patient outcome vs. clinical and transplant variables at the Nairobi Hospital

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Variable		Number alive	Number dead	p value
Age	≤ 40	13	6	0.483
	> 40	15	11	
Gender	Male	24	8	0.006*
	Female	4	9	
Co-morbidity	Yes	16	12	0.367
	No	12	5	
Readmission	Yes	14	15	0.012*
	No	14	2	
Finances	Stable	23	4	0.003*
	Unstable	1	5	
Compliance	Yes	24	6	0.095
	No	2	3	
Mean Creatinine (mmols)		185 ± 195	548 ± 676	0.002
ESRD Cause	CGN	5	7	0.163
	Other	23	10	
	Diabetes/HTN	8	5	0.952
	Other	20	12	
Follow-up	≤ 1 yr	4	10	0.003*
	> 1 yr	24	7	

* Fischer's exact test, HTN- hypertension, CGN- chronic glomerulonephritis, ESRD- End stage renal disease.

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Table 2: Graft outcome vs. clinical and transplant variables at the Nairobi Hospital

Variable		Graft Survived	Graft Lost	p value
Readmission	Yes	10	19	0.005*
	No	13	3	
HTN/Diabetes	Yes	6	7	0.672
	No	17	15	
Age	≤ 40	12	7	0.167
	> 40	11	15	
Survival duration	≤ 1yr	2	11	0.003*
	> 1yr	21	11	
Gender	Male	21	11	0.003*
	Female	2	11	
Rejection episode	Yes	3	10	0.016
	No	20	12	

• Fischer's exact test; HTN- hypertension

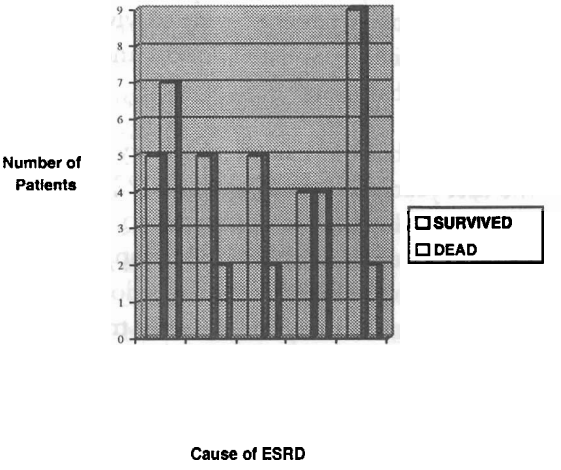
There were significantly fewer deaths among male recipients (8 out of 32). Conversely, the overall mortality was higher for female graft recipients (9 out of 13, p = 0.008). Figure 1 depicts the overall Kaplan-Meier plot of survival and the effect of different genders on the survival curve.

The other factors that adversely affected patient survival following transplantation included elevated serum creatinine levels (indicating sub-optimal graft function), readmissions (with various ailments or rejection), and lack of sustainable finances hence poor compliance with therapy (Table 1). There were no significant differences between survivors and non-survivors with respect to age of recipient at the time of transplantation and the presence of co-morbid disease (Table 1).

In roughly half of the kidney transplant recipients the cause of renal failure was chronic glomerulonephritis or diabetic kidney disease (chronic glomerulonephritis 26.7%, diabetes 22.2%, hypertension 15.6%, nephro/glomerulosclerosis 15.6%, miscellaneous 19.9%). The age and gender differences between the different diagnostic categories were not statistically significant.

The proportion of non-survivors appeared higher in those recipients with primary glomerulonephritis (58.3%) than the other indications for transplantation (Hypertension 28.6%, Diabetes 28.6%, nephro/glomerulosclerosis 50%, others 18.2%)(Fig.2). These observations were however not significant in statistical terms (Table 1). The overall graft survival was 77.8 % at 1year and 52.7 % at 5 years. The female recipients had significantly worse graft outcome than males (p=0.002). Graft outcome was also adversely affected by occurrence of at least an episode of acute rejection, readmission and duration of follow-up less than one year (P< 0.05). On logistic regression, rejection episodes had the most influence on graft survival.

Fig. 2 Patient Outcome Versus Cause Of ESRD at Nairobi Hospital



We found that there were no statistically significant differences in graft survival with respect to recipient age and presence of co-morbid disease (Table 2). Six recipients died of chronic allograft rejection **while** another six succumbed due to sepsis. There were two operative deaths, two cardiovascular and one death due to malignancy

Discussion

This study provides results of long-term follow-up of patients undergoing renal transplantation in a single center in Africa. The follow-up rate of 74 %, although less than would be expected in a similar study in developed countries, is a high figure for Africa. The rate is expected to be much lower in public programs where financial and other social impediments are greater. Transplantation programs are available in only a few countries in Africa (10). To the best of our knowledge, our results represent the first long-term outcome results following kidney transplantation in Kenya and the East and Central Africa region.

Our results indicate that the overall mortality for living donor transplant recipients was 10.7 per 100 person years. The one and five year survival figures were 77.8 and 63.1 percent respectively. These figures depict higher mortality figures in comparison with

those from the industrialized countries. The survival of patients undergoing renal transplantation has improved considerably in the latter countries over the past three decades with expected survival rates of 95 percent at 1 year and around 90 percent at 3-5 years[1]. Although our figures appear to approach the results of the industrial World in the 1970s when 1-year survival figures were 85 percent for the young and 60% for older transplant recipients[1], recent results from some large-volume centers convinces us that good outcome is possible in African hospitals. Analyzing over 4,000 kidney allograft recipients from the Brazilian renal Transplant registry, Sesso and his colleagues found patient 5-year survival rates of 69 percent for living unrelated donors and 73.2 percent for cadaveric donors[11].

We found that the risk of mortality was higher in the first year after transplantation (22.2/100 patient years of follow-up) as compared to the later years (5.79/100 person years of follow-up). This finding conforms to the results of studies done elsewhere[2]. In a Netherlands study of 1002 renal transplantations performed between 1966-1994, the crude mortality rate for living donor kidney transplant recipients was 3.7 per 100 person years of follow-up in the first year and 0.9/100 person years of follow-up thereafter.

The higher mortality in the first year is thought to be due to transplant procedures, intensity of immunosuppression and related complications[2]. In our earlier analysis of the first 50 kidney recipients, twenty-eight patients (56.0%) had at least one complication, 28.0% had at least a rejection episode and seven died during the first 30 days after transplantation. They died of sepsis, surgical complications, and immunosuppression-related complications[9].

Our results showed that male recipients and patients with sustainable finances had better survival than female recipients and those without sustainable income. The finding on financial sustainability is not surprising as the immunosuppressive regimens to prevent and control rejection nephropathy are expensive. The implication of this finding to the development of national transplant programs in the African continent is that the programs will fail if allocation of funds by governments will not be sufficient. The majority of those on transplant waiting lists are poor and hence lacking in both employer support and health insurance to afford immune therapy.

Although conflicting results have been published[12,13,14,15] with regards to long-term survival, better 5-year patient survival with the use of cyclosporin continues to be reported[14]. The finding that male recipients have higher survival is in contrast with other studies. Females have higher patient and graft survivals in Netherlands as compared to males[2,16]. We could find no obvious explanation for the superior survival in males. The smaller proportion of co-morbidity and rejection nephropathy in males as compared to female recipients may be part of the explanation. There was an instance where a female patient discontinued her immunosuppressive regime because the financier husband had lost his job.

The other factors that were related to adverse patient outcome were elevated serum creatinine levels and being readmitted. Elevated creatinine levels denote diminishing kidney function (rejection). These factors are related and would have confounding effects on each other. It was not surprising then that with regression analysis, only readmission remained as the independent predictor of mortality.

The age of the patients and the presence of co-morbid disease as well as the underlying cause of end-stage renal failure did not have any statistical effect on overall survival- a finding that contrasts other results. Higher mortality rates have been reported for patients aged 40 years and above, both within and after the first year of transplantation[16,17]. Although small, Arend et al, found a higher risk of mortality in the presence of diabetes and hypertension[2]. The number of kidney recipients we have followed is small. A larger pool of patients may give a different picture. It is also possible that the results extend those of Meier-Kriesche et al.[18]. The authors found recipient age was a risk factor for development of chronic allograft failure in Caucasians and not African-Americans.

The one and five-year graft survival was 77.8 and 52.7 percent respectively. These survival figures are lower than in the West. The 1-year graft survival rate is 90% for recipients of living donor kidneys and 77% for cadaver donor kidneys[19]. In USA, between 1988-1996, survival rate at 1 year for transplants from living donors increased from 88.8% in 1988 to 93.9% in 1996 (increase of 5.1 percentage points)[4]. Graft loss after transplantation may be due to acute rejection, primary non-function, graft thrombosis, recurrent kidney disease or death of patient with functioning graft.

Our results indicate that the factors that had significant detrimental effect on survival of renal

allografts were rejection episodes, readmission, female gender, and patient survival of less than one year. In the USA study, clinical acute rejection within the first year after transplantation had a detrimental effect on long-term graft survival[4].

The pathogenesis of chronic allograft nephropathy is the entry point for strategies to prevent late allograft failure. Early allograft damage caused by acute peritransplantational injuries and episodes of acute rejection result in loss of functional nephrons. Thereafter both immunologic and non-immunologic factors (poor HLA matching, sub-optimal immunosuppression, non-compliance of patient, older donor, hypertension, cyclosporin toxicity) contribute to the development of chronic allograft nephropathy[7].

The current strategies to prevent allograft rejection should then include peri-operative management, prevention of acute rejection, treatment of severe rejection, and optimization of drug dosages beyond the first year and the treatment of hypertension. Optimal donor selection, shortening of cold ischemia and preferential use of living donors are the current vogue[20,21]. Newer immunosuppressive drugs (Tacrolimus, Mycophenolate Mofetil, Sirolimus, Monoclonal antibodies against interleukin-2 receptor) have reduced the incidence of acute rejection among recipients of renal allografts to as low as 10-30%[22] and it is anticipated that this lowered frequency will translate into decreased incidence of allograft loss. It has been shown in other studies also that acute rejection is an important predictor of chronic allograft nephropathy[23,24].

This study has several limitations. Retrospective analyses suffer from inherent flaws of missing data and author biases. Our results are from a medium sized private hospital in Nairobi, where the usual problems of limited resources for patient care are minimal. Its external validity can be questioned. Results from the public sector are necessary to confirm possibility of good surgical outcome. We have not analyzed patients on dialysis treatment to demonstrate survival advantage of renal transplantation in this setting. Additionally other factors known to influence both patient and graft survival including surgical procedures, duration of cold ischaemia and dialysis treatment have not been considered in the analysis. Future prospective studies to validate the results presented are necessary.

Conclusion

Patient survival following renal transplantation was 77.8 percent and 63.1 percent at one and five years after transplantation respectively, with overall mortality rate of 37.8 percent (10.7 per 100 person-years). Survival was a function of recipient gender, post-operative kidney function and sustainable finances. Graft survival was 77.8 percent at one year and 52.7 percent at five years. Rejection episodes were the major risk factor for poor graft outcome.

It would seem that our ideal patient for kidney transplantation was a male with adequate financial resources to keep the kidneys in optimal function after transplantation. Pharmacologic manipulations including the use of newer immunosuppressive regimens may reduce allograft loss and should impact positively on patient survival.

The outcome results appear inferior to figures from the developed economies. Higher mortality during the early months after transplantation corroborates other studies. Other results indicate a protective effect of the female gender. Our small sample size could partly explain the minimal effect of gender and co-morbidity on outcome. The effect of sustainable finances has implications on the development of transplant programs in the continent.

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References

1. Briggs JD Causes of death after renal transplantation Nephrol dial Transplan 2001 16: 1545-1549
2. Arend SM, Mallat MJK, Westendorp RJW, van der Woude FJ and van Es LA. Patient survival after renal transplantation; more than 25 years follow-up Nephrol Dial Transplant 1997; 12: 1672-1679
3. Merion RM, White DJG, Thiru S, Evans DB, Calne RY. Cyclosporine: five years' experience in cadaveric renal transplantation. N Engl J Med 1984; 310:148-154
4. Hariharan S., Johnson CP, Bresnahan BA, Taranto SE, Mcintosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988-1996 N. Engl. J. Med 2000; 342: 605-612
5. Sollinger HE. Mycophenolate mofetil for the prevention of acute rejection in primary

cadaveric renal allograft recipients. Transplantation 1995; 60: 225-232

6. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. Comparison of Tacrolimus (FK506) and cyclosporin for immunosuppression after cadaveric renal transplantation. Transplantation 1997; 63: 977-983
7. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi B. Strategies to improve long-term outcomes after renal transplantation New Engl J Med ; 346: 580-590
8. Saidi H. Fifty consecutive renal transplants- An audit; Part III- Experience with living donors The Nairobi Hospital Proceedings 2001; 5:65-68
9. Saidi H and Kabiru J. Fifty consecutive renal transplants- An audit; Part II- 30 day mortality and morbidity The Nairobi hospital proceedings 2001; 5: 21-28
10. Magoha GAO and Ngumi ZWW. Renal Transplantation during the twentieth century; a review East. Afr. Med. J. 2001; 78(6): 317-321
11. Sesso R, Josephson MA, Ancao MS, Draibe SA, Sigulem D. A retrospective study of kidney transplant recipients from living unrelated donors. J. Amer. Soc. Of Nephr. 1998 9(4): 684-701
12. Kootte AMM, Lensen LM, van Es LA, Paul LC. Controlled cyclosporine conversion at three months after renal transplantation. Transplantation 1988; 46: 677-680
13. Hollander AAMJ, vans Saase JLCM, Kootte AMM et al. Beneficial effects of conversion from cyclosporin to Azathioprine after kidney transplantation. Lancet 1995; 345: 610-614
14. Stiller CR, Opelz G. Should cyclosporine be continued indefinitely? Transplant Proc 1991; 23: 36-40
15. Paul LC, Sutherland F, Klassen J, buckle S, Burgess E. Cardiovascular risk impact of cyclosporine immunosuppression in renal transplant recipients. Transplant proc 1992; 24:2740-2741
16. Perez RV, Matas AJ, Gillingham KJ et al. Lessons learned and future hopes: three thousand renal transplants at the university o f Minnesota. In: Terasaki PI, Cecka JM (eds). Clinical transplants 1990. UCLA Press, 1990; 217-231
17. Nyberg G, Nilsson B, Norden G, Karlberg I. Outcome of renal transplantation in patients over the age of 60 years; a case-control study. Nephrol Dial Transplant 1995; 10: 91-94
18. Meier-Kriesche HU, Ojo AO, Cibrik DM, Hanson JA, Leichtman AB, Magee JC, Port FK, Kaplan B. Relationship of recipient age and development of chronic allograft failure. Transplantation 2000; 70(2): 306-310
19. Riehle RA, Steckler R, Naslund EB, Riggio R and Cheigh J et al. Selection criteria for the evaluation of living related renal donors. J. Urol. 1990; 144:845-848
20. Gjertson DW, Cecka JM. Living unrelated donor kidney transplantation. Kidney Int. 2000; 58: 491-499
21. Troppman C, Gillingham KJ, Benedetti E, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. Transplantation 1995; 59: 962-968
22. Denton MD, Magee CM, Sayegh MH. Immunosuppressive strategies in transplantation. Lancet 1999; 353; 1083-1091
23. Almond PS, Matas A, Gillingham K et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation 1993; 55: 752-757
24. Monaco AP, Burke JF Jr, Ferguson RM, et al. Current thinking on chronic renal allograft rejection: issues, concerns, and recommendations from a 1997 roundtable discussion. Am J Kidney Dis 1999; 33: 150-160