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ORIGINAL ARTICLE

OUTCOME OF RENAL ALLOGRAFT RECIPIENTS AT SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE KIDNEY TRANSPLANT CENTER, ADDIS ABABA

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ABSTRACT

Introduction: *Kidney transplant is the current modality of choice as a renal replacement therapy due to superior patient survival and quality of life than both peritoneal and hemodialysis. The service is limited outside of developed countries due to the requirement for structured organization, extended expertise, and qualified supportive laboratory, as well as extensive health system service support in general.*

Objective: *The aim of the study is to describe renal allograft recipient outcomes during the first two years following establishment of the national kidney transplant center in Addis Ababa, Ethiopia.*

Methods: *A review of the case records of all recipients of renal allografts at Saint Paul's Hospital Millennium Medical College between September 2015 and August 2017 was done.*

Results*: Fifty two live donor kidney transplants were performed over two years. The cause of native kidney diseases was unknown in majority (32.6%), while chronic glomerulonephritis accounted for 30.8%. One fourth of recipients were transfused at least once before transplant. There was no biopsy proven rejection episode. There was one early graft loss from unknown cause. At least one organ system was affected with drug side effects in nearly in all (96%), leucopenia occurring in one fourth (22%) was very serious. Death censored graft survival at one year is 97.5% while mean GFR at one week, three month, six month and one year was 73.1, 93.6, 95.6, and 96ml/min, respectively. After successful kidney transplant pre-transplant hypertension subsided in 46.5% of patients.*

Conclusion: *Graft survival and graft function at one year were excellent, and comparable to well reputed centers worldwide.*

Key words: *Ethiopia, kidney, transplant, outcome*

INTRODUCTION

For those patients with ESRD, dialysis is often the only option, although renal transplantation is the treatment of choice, with better long-term survival and quality of life.

The introduction of calcineurin inhibitors has significantly reduced first year graft loss, while improvements in optimal use of immunosuppressants has improved patient survival (1).

The first-year graft and patient survival is best with a living-related fully matched DSA negative and ABO compatible young allograft recipient from a young male in a good outcome center.

Outcomes are somewhat lower for the recipient of a deceased renal allograft recipient. A report from WHO in 2018 outcome of organ transplant on one year graft survival across the world is depicted Figure 1 below (2,3).

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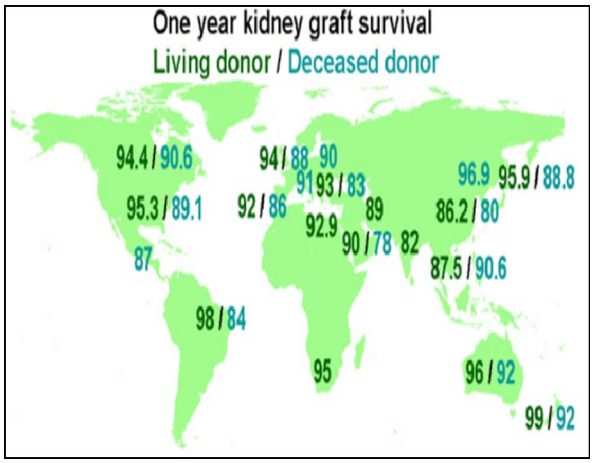

Figure 1: WHO 2018 outcome of organ transplant

The average graft function six months post-transplant from a report of the United States (US) Kidney Transplant Database in 2010 was 58.0 (47.0,70.7), mL/min/1.73 m2 while percent of acute rejection in the first six months and percent of patients requiring dialysis during the first week was 8.5% and 3.2%, respectively. These outcomes were worse for black Americans (4,5).

Recipients of ABO compatible living-related kidney transplants are more likely to receive a less intense induction and maintenance immunosuppression. This practice decreases the frequency of infectious, cardiovascular, malignant, and other complications. In addition to the common bacterial infections, cytomegalovirus, and BK virus, fungal infections and post-transplant tuberculosis is common and a challenge in developing countries. Tharayil GJ reported the three-year post-transplant tuberculosis in 1,414 renal allograft recipients to be 13.3%. Of 166 patients who developed post-transplant tuberculosis 53 died (6-8).

Renal transplant services have largely been limited to developed countries, due to requirement for structured organization, extensive expertise, and qualified supportive laboratory services. Because of these requirements, only a few African countries have initiated transplant services. Ethiopia started a renal transplant service in 2015 at the national kidney transplant center (9).

This study was performed with intent of describing outcome of renal transplant recipients of the first two years at St. Paul Hospital's Millennium Medical Colleges (SPHMMC) National Kidney Transplant Center of Ethiopia to create understanding of how acceptable outcomes are and depict peculiar features of the center.

PATIENTS AND METHODS

The study was conducted in SPHMMC National Kidney Transplant Centre, Addis Ababa, Ethiopia. The transplant center was established in 2013 under the Federal Ministry of Health in collaboration with University of Michigan. A multidisciplinary team of specialists was developed that included surgery, nephrology, cardiology, radiology, pulmonology, endocrinology and others. Fifty two end stage kidney disease (ESRD) patients selected with prespecified selection criteria in intermediate risk of rejection got a renal transplant in the first two years of transplant service.

All patients received an induction therapy of basiliximab 20mg intravenous (IV) on days one and four. Methylprednisolone 500mg iv in the operation theater followed by 250mg iv, 80mg iv, 60mg per os (po), and 40mg po on post op day1,2,3 and 4, respectively, was given to all. Maintenance therapy included Tacrolimus (Pangraf), mycophenolate (CellCept) and prednisolone. Prednisolone was tapered to 5mg by the end of first month, while tacrolimus was maintained 8-12ng/lit in the first two months, 5-10ng/dl two to three month and 5-8ng/dl after wards. CellCept was initiated 2 days before transplant and maintained as 1gm twice a day.

Prophylaxis for bacterial, viral, fungal and tuberculous infections were given to all as cotrimoxazole 960mg po/d for a year, valgancyclovir of 900mg po/d for three months, nystatin oral gel four times a day for one month and isoniazid 300mg for six months. Dose and duration of prophylaxis medications were modified as necessary. The mean follow-up was 22months (11 to 36 months) with 92% followed for more than a year excluding patients who died. No patient was lost from follow up.

RESULTS

The first recipient was an elderly male. Since then, a total of 52 transplants were performed over two years; 41 (78.8%) of the recipients were male and given care mainly by the spouse (38%) during transplant (Table 1). All kidneys were collected from live donors, mostly blood related (89%) to the recipients, with 46% being sibling donors. Most donors were below the age of 45(75%); 23% were below the age of 25. HLA typing and CDC cross match was done for all patients. CDC was negative for all recipients, and DSA was either negative or not performed. HLA typing revealed the following: three zero mismatch, 10 (20.4%) halo match, and 10 three mismatch. Only three were six mismatch. No patient had a prior organ transplant, while 25 (48%) have received blood transfusions, and three of the 11 female recipients had at least one pregnancy.

Table 1: Socio-demographic characteristics of live donor kidney transplant recipients, SPHMMC*, Addis Ababa, Ethiopia. September 2015 to August 2017.

Variable		Number	Percent
Sex	Male	41	78.8
	Female	11	11.2
	Total	52	100
Age group (years)	18-25	8	15.4
	25-45	36	69.2
	45-65	8	15.4
	>65	0	0
	Total	52	100
Residence	AA	37	71.2
	Outside Addis	15	28.8
Marital status	Single	19	36.5
	Married	28	53.9
	Divorced	4	5.8
	Widowed	2	3.9
	Total	52	100.0
Occupation	Employee	20	40.0
	Personal business	11	22.0
	Jobless	7	14.0
	Other	12	24.0
	Total	50	100.0
Literacy status	Cannot read and write	2	4.0
	Read and write	2	4.0
	Primary complete	13	26.0
	High school complete	20	40.0
	College graduate	13	26.0
	Total	50	100
Care Giver	Mother and father	14	29.8
	Spouse	18	38.3
	Lives alone	1	2.1
	Other	14	29.8
	Total	47	100

Very few patients had clear cause for native kidney dysfunction, although the following causes were noted: lupus nephritis (2%), diabetic nephropathy (5.8%), hypertensive nephrosclerosis (7.7%), and ADPKD (2%). The most common cause was unknown(32.6%) or probable chronic glomerulonephritis (30.8%). Five percent of patients had a preemptive transplant (5.8%), while 10% had more than two years of hemodialysis.

Of note, while 35% of patients have BMI of less than 18.5% at the time of transplant, only 7.7% have BMI below 18.5 at one year of transplant. No single patient had a biopsy proven rejection episode; all renal biopsies with suspected rejection turned out to be ATN.

Four patients were empirically treated for a possible rejection, all with pulse dose methyl prednisolone with graft function returning to baseline.

Nineteen patients had at least one episode of infection requiring antibiotic use. GI and urinary tract were the most frequently affected organ systems. There were nine severe bacterial infections (pneumonia, sepsis, etc...) for which patients required hospital re-admission after transplant. Three patients were treated for CMV infection, while one for BKV nephropathy. Only one recipient developed tuberculosis after transplant. He successfully completed a six-month course of treatment. The patient's requirement for tacrolimus increased during treatment with INH, rifampicin, ethambutol and pyrazinamide.

New onset diabetes after transplant developed in 7.69%, while 36.5% developed post-transplant erythrocytosis. Hypertension was present in (86.5%) of recipients prior to transplant, with resolution in (46.7%) after kidney transplant. Only one patient developed a new onset hypertension after transplant. No patient required transfusion after transplant.

Nearly all patients reported (96.2%) at least one drug related side effect. GI upset was the most common (47%), followed by dermatologic complications (32.7%), hematologic complications including leukopenia (22%), transaminitis (16%), and nephrotoxicity (10%). One patient discontinued cotrimoxazole early for allergy, while three patients discontinued INH for severe transaminitis.

Only one patient reported failing to take medications at a prescribed dose and schedule for at least six days a week.

One-year death censored graft survival was 97.9%, with only one recipient losing the allograft early. The mean graft function at one week, three months, six months, and one year following transplant was 73.1, 93.6, 95.6, 96 and 83.3ml/min, respectively. Only 12% of patients had stage 3 CKD the one-year post-transplant. The following bar graph shows proportion of patients with specific stages of graft function at different time from transplant. (Figure 2).

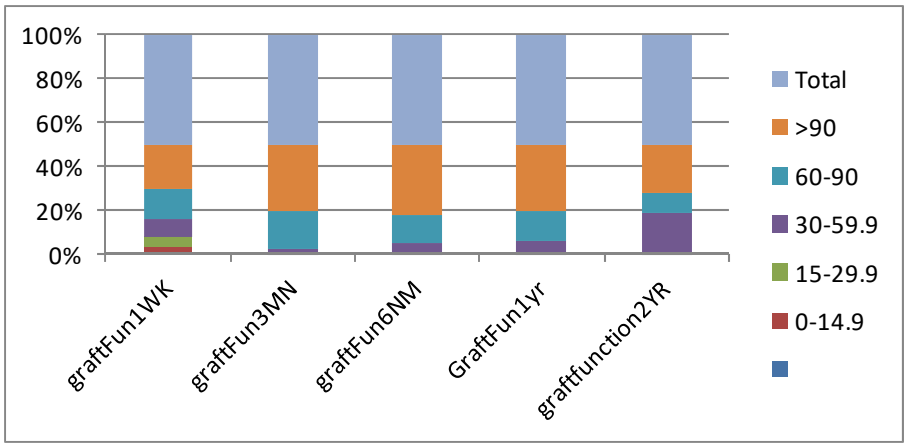

Figure 2: Graft function at different time from kidney transplant of live donor kidney

There were four deaths in the first-year post-transplant with serious infections being the cause for all. Two had CMV infection, while the third had infective endocarditis and the fourth patient had uncontrolled graft pyelonephritis. One-year patient survival is 92.3%. On logistic regression, 3 HLA mismatch [AOR=27(95% CI: 1.26- 578.354)] and pre-transplant transfusion [AOR=23(95%CI: 1.396-378.898)] were independent predicators of worse outcome.

DISCUSSION

Transplant has succeeded as the prime choice for ESRD care in Africa. Ethiopia has joined as the fifteenth country to successfully establish a kidney transplant service. A large proportion of our patients had unclear cause of the native kidney disease, a result of limited renal service in general.

The proportion of patients with diabetic nephropathy and hypertensive nephrosclerosis was low, due to a selection bias for younger patients with less comorbidities. As the center is new, the first patients were intentionally closer to ideal candidates.

We reported a very low number of preemptive transplants compared to a report made by Colleen et al. This may be attribute to the fact that our center is new, and patient backlog was significant. The long waiting time for transplant service once having a designated kidney donor, as well as late presentation to the health care system, are designated targets of intervention once service expansion is realized (10).

No single patient experienced biopsy proven rejection episode, although we treated four patients empirically. This was amazingly low especially compared with other center experience, although may have results from a conservative approach to histocompability. In a Nigerian report of 47 patients followed for three years with same maintenance immunosuppression regimen as recipients in our center, the reported incidence of rejection was 29.8%. Though the two populations are similar in terms of native kidney disease, triple immunosuppression and relatively young recipients the difference in rate of rejection is significant. Differences between these two studies, particularly as a possible reason for differing rejection rates, includes a higher rate of unrelated donors and lower rates of drug level monitoring in the Nigerian study, particularly as our center utilized mostly related donors with good matching, regularly monitored tacrolimus level, had aggressive approach to adherence monitoring and follow (11).

The susceptibility for infections due to active immunosuppression from tacrolimus MMF and prednisolone couple with drug related leucopenia/neutropenia predisposes these patients for serious infections. The usual sanitary parameters including food hygiene, waste disposal and clean and safe water are limitations that place special risk for these patients, although the physicians and transplant team have risen to challenge. These problems, coupled with the lagging microbiology and infectious disease specialty services in the country in general and our hospital, pose serious challenges to patient survival.

Post-transplant CMV infection was very serious, as two out of three of the patients with CMV disease died despite a preserved graft function. All CMV disease occurred after recipients completed a three-month valgancyclovir prophylaxis. The rate was higher than reported from USA for late onset CMV disease (4%). It is possible that the low rejection rate is the counterbalance to the infection and CMV rate. Regular monitoring can reduce these serious infections (12).

The prevalence of tuberculosis was 2%, which is very low for tuberculosis given the higher burden expected, since many report incidences as high as 15%. The use of INH preventive therapy for all recipients tolerating it helps to explain these outcomes (13).

The incidence of NODAT was similar with worldwide estimate, but it is low as compared to a report from Cape Town of 18%. Early tapering of steroid to maintenance dose, regular monitoring of CNI's and relatively younger recipient age may have contributed to our rate (14).

Almost all patients have hemoglobin values more than 11gm/dl and post-transplant erythrocytosis was present in 36.5%. Addis Ababa lies 3000meterabove sea level, and is known for champion athletes, which can be a major factor for this finding.

When compared with a rate of less than 5% normotensives in an Italian report, post-transplant hypertension was very low, and with resolution in 46.7%, representing a secondary hypertension that subsided in correcting renal function (15). Despite these findings, and as tacrolimus can cause hypertension long term, we continue to monitor these patients.

Leucopenia is a common and frustrating complication of valgancyclovir and mycophenolate. The prevalence was marginally higher than reported figures of 10-15%.In a 64 individual report who received MMF and valgancyclovir, the rate was 20%. These complications have been major reason to discontinue valganciclovir prophylaxis and hold MMF for a while until recovery (16).

Of all outcome measures that one looks at after kidney transplant, graft function is of paramount importance. Since kidney transplant first developed, first year graft survival has reached its peak. Many experienced centers enjoy a graft survival of 98% or more for live donor ABO compatible kidney transplant. According to the 2017 WHO report, across the globe the best 1year graft survival for live donor kidney transplant was 99% while the worst 82%, and most countries had between 90 and 94%. Our center has enjoyed a death censored graft survival rate of 97.5%, which compares favorably with the best. Average graft function was also good with a glomerular filtration rate (GFR) of 96ml/min. Proper patient selection, protocol-based immunosuppression and prophylaxis, and a motivated home team working in harmony with experts from the University of Michigan and frequent mentoring of Ethiopian nephrologists by US nephrologists has contributed to this outcome (3).

Conclusion

Ethiopia's first transplant center has demonstrated excellent graft and patient survival, with good graft function for those ESRD patients, who were transplanted. Rejection rates were low, although this may have been at the expense of increased CMV infections. As the nascent transplant center further develops, we will continue to analyze our results to optimize care of the expanding post-transplant patient population.

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Competing Interest:
The authors declare that this manuscript was approved by all authors in its current form and that no competing interest exists.

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